VOL. 37 JUNE 1961 NO. 6

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

EDWARD A. GALL

R. R. NEWELL

FERDINAND F. McALLISTER

COMMON UROLOGICAL PROBLEMS IN GENERAL PRACTICE

Transcription of a Panel Meeting on Therapeutics

VICTOR F. MARSHALL
FRANK C. HAMM
SIMON A. BEISLER
RALPH J. VEENEMA

Optimal Asthma Relief

from smallest dosage...

in briefest time

Medihaler®

automatically controlled dosage by aerosol administration

22½% more vital capacity within seconds

The suspension of premicronized dry particles assures maximum delivery of the medication to the alveolar spaces where the therapeutic effect is exerted. The Medihaler suspension affords 5 times the bronchodilating power of the same medication in solution and approximately 20 times that of a squeeze bulb nebulizer.

Medihaler is available with either of the two outstanding bronchodilating agents:

Medihaler-ISO® (isoproterenol)

Medihaler-EPI® (epinephrine)

NEW! 30 cc size vial for office or home

Riker Northridge, California

phenyramidol HCl

analexin®

relieves the total pain experience

anytime

for relief of arthritic pain For the patient whose condition requires continuous pain relief, Analexin provides analgesia that is safe and effective. In effectiveness, Analexin's analgesic action is within the range of codeine, yet Analexin is non-narcotic and not narcotic related, and there is no evidence suggestive of tolerance or cumulative toxicity.[1-8] In fact, Analexin is so safe that dosage may be hourly if necessary, depending on the degree of pain relief required.

When you prescribe Analexin for arthritic pain, the clinical evidence of its efficacy stands behind your decision. What better reason for reserving a place for Analexin in your armamentarium?

"*...There is no question that the predictability of satisfactory control of a painful state is high and that the occurrence of untoward reactions is low.*"[1]

*Patients who failed to respond include severe active rheumatoid arthritis cases not responding to any analgesic dosage scheme.

Analexin®—*for relief of pain.* Each tablet contains 200 mg. phenyramidol HCl. *Dosage:* Generally, 2 tablets at onset of pain followed by 1 or 2 tablets at intervals of 1 to 4 hours, as needed.

Analexin-AF®—*for relief of pain complicated by inflammatory processes.* Each tablet contains 100 mg. phenyramidol HCl and 300 mg. aluminum aspirin. *Dosage:* Generally, 2 tablets at onset of pain followed by 1 or 2 tablets at intervals of 1 to 4 hours, as needed.

Analexin® Syrup—*new convenient dosage form for children and adults.* Each 5 cc. contains phenyramidol salicylate 100 mg. *Dosage:* Children—under 3 yrs., 1 tsp. 3 or 4 times daily; 3-12 yrs., 2 tsp. 3 or 4 times daily. Adults—2 to 4 tsp. every one to 4 hours.

1. Batterman, R. C.: Ann. New York Acad. Sc. *86*:203, 1960. 2. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960. 3. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 4. O'Dell, T. B., *et al.*: Fed. Proc. *18*:1694, 1959. 5. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4347, 1959. 6. Wainer, A. S.: Clin. Med. *7*:2331, 1960. 7. Clinical data from the files of the Medical Dept., Irwin, Neisler & Co., 1959. 8. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959.

Neisler *IRWIN, NEISLER & CO., Decatur, Illinois*

Acts within minutes—KOAGAMIN, unlike other hemostatic agents, acts *quickly* in *minimal* dosages. Working on the late phases of the clotting mechanism, KOAGAMIN does not require massive and prolonged pre- or postoperative dosages to control capillary and venous bleeding.

Acts with predictable safety—In 20 years of clinical use, no toxic or side actions have been reported with KOAGAMIN. Bleeding is arrested without danger of thrombosis, and because KOAGAMIN contains no protein or alkaloid, it can be administered without danger of sensitization or untoward reactions.

Acts effectively in a broad range of indications—Because of its *unparalleled safety* and *outstanding effectiveness*, KOAGAMIN has been successfully employed in...hemorrhagic diseases, abnormal bleeding, blood disorders, surgical cases and trauma.

KOAGAMIN, an aqueous solution of oxalic (5 mg. per cc.) and malonic (2.5 mg. per cc.) acids for parenteral use, is supplied in 10-cc. diaphragm-stoppered vials.

CHATHAM PHARMACEUTICALS, INC · NEWARK 2, NEW JERSEY

Distributed in Canada by Austin Laboratories, Limited, Guelph, Ontario

Chatham

BEFORE, DURING AND AFTER SURGERY

KOAGAMIN®

(parenteral hemostat)

controls bleeding with minimal dosage and maximum safety

10360

The Bulletin of The New York Academy of Medicine. Vol. 37, No. 6, June, 1961. Published Monthly by The New York Academy of Medicine, 2 East 103 Street, New York 29, N. Y. Entered as second-class matter February 3, 1928, at the Post Office at New York, N. Y., under the act of August 24, 1912. Postage paid at New York, N. Y. Annual subscription United States and Canada $8.00. All other countries $9.00. Single copies 90c.

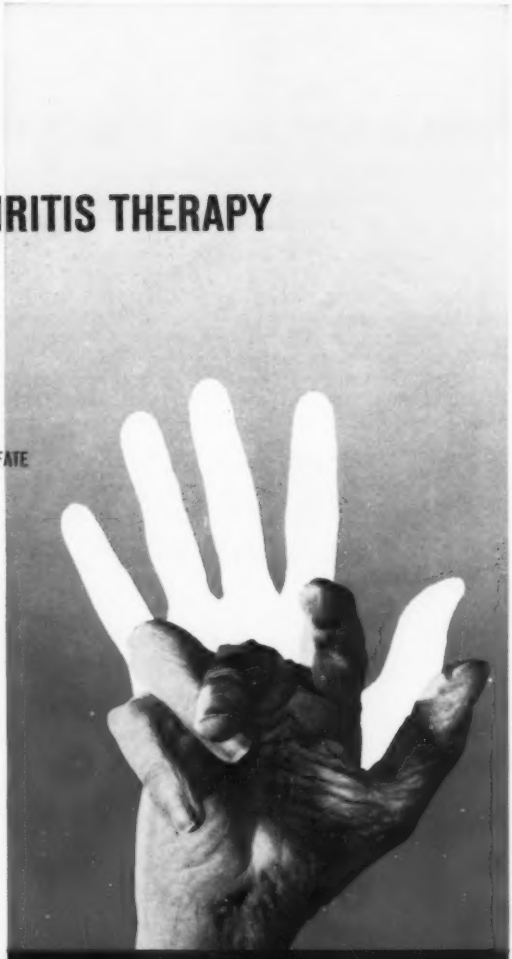
MAINSTAY

OF RHEUMATOID ARTHRITIS THERAPY

Plaquenil® SULFATE

Brand of hydroxychloroquine sulfate

New Long Term Chemotherapy of **RHEUMATOID ARTHRITIS**



"Whatever else may be needed from time to time in the management of individual cases, these drugs [Plaquenil and Aralen] should always be given a prolonged trial (at least six months) as the 'mainstay' of therapy."

Bagnall, A. W. (Univ. British Columbia, Vancouver, B. C.): A.M.A. Clinical Meeting (Scientific Section, Exhibit No. 124), Minneapolis, Minnesota, Dec. 2-5, 1958.

"The 4-aminoquinoline drugs (Plaquenil and Aralen) together with supplemental agents administered in nontoxic doses effectively maintained suppression of the disease in 83 per cent of 194 patients followed for 18 months."

Scherbel, A. L.; Harrison, J. W., and Atdjian, Martin: **Cleveland Clin. Quart.** ***25:95, April, 1958.***

"When used in tolerated dosage and over a sufficient period of time, there appears to be a tremendous therapeutic potential in the antimalarial drugs. . . . Plaquenil in this study did not have as many side effects as Aralen and thus appears to be a more practical compound."

Cramer, Quentin (Kansas City): **Missouri Med.** ***55:1203, Nov., 1958.***

Plaquenil is the hydroxy derivative of Aralen® and is available as Plaquenil sulfate in tablets of 200 mg. (bottles of 100).

Average Dosage:

INITIAL—400 to 600 mg. (1 tablet 2 or 3 times daily)

MAINTENANCE—200 to 400 mg. (1 tablet once or twice daily)

Write for Plaquenil booklet discussing clinical experience, dosage, tolerance, precautions, etc., in detail.

Winthrop LABORATORIES • New York 18, N. Y.

Plaquenil (brand of hydroxychloroquine) and Aralen (brand of chloroquine), trademarks reg. U.S. Pat. Off.

1427 M

when allergy looms large in the life of your patient...

BENADRYL provides a twofold therapeutic approach to the management of distressing symptoms of grass-pollen allergy ■ **antihistaminic action** relieves nasal congestion, sneezing, lacrimation, and pruritus ■ **antispasmodic action** affords relief of bronchial and gastrointestinal spasm.

BENADRYL Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is available in a variety of forms including: Kapseals® of 50 mg.; Capsules of 25 mg.; Emplets® (enteric-coated tablets) of 50 mg.; in aqueous solutions: 1-cc. Ampoules, 50 mg. per cc.; 10- and 30-cc. Steri-Vials,® 10 mg. per cc.; Elixir, 10 mg. per 4 cc.; 2% Ointment (water-miscible base); Kapseals of 50 mg. BENADRYL Hydrochloride with 25 mg. ephedrine sulfate. *Precautions:* Avoid subcutaneous or perivascular injection. Single parenteral dosage greater than 100 mg. should be avoided, particularly in hypertension and cardiac disease. Products containing BENADRYL should be used cautiously with hypnotics or other sedatives; if atropine-like effects are undesirable; or if the patient engages in activities requiring alertness or rapid, accurate response.

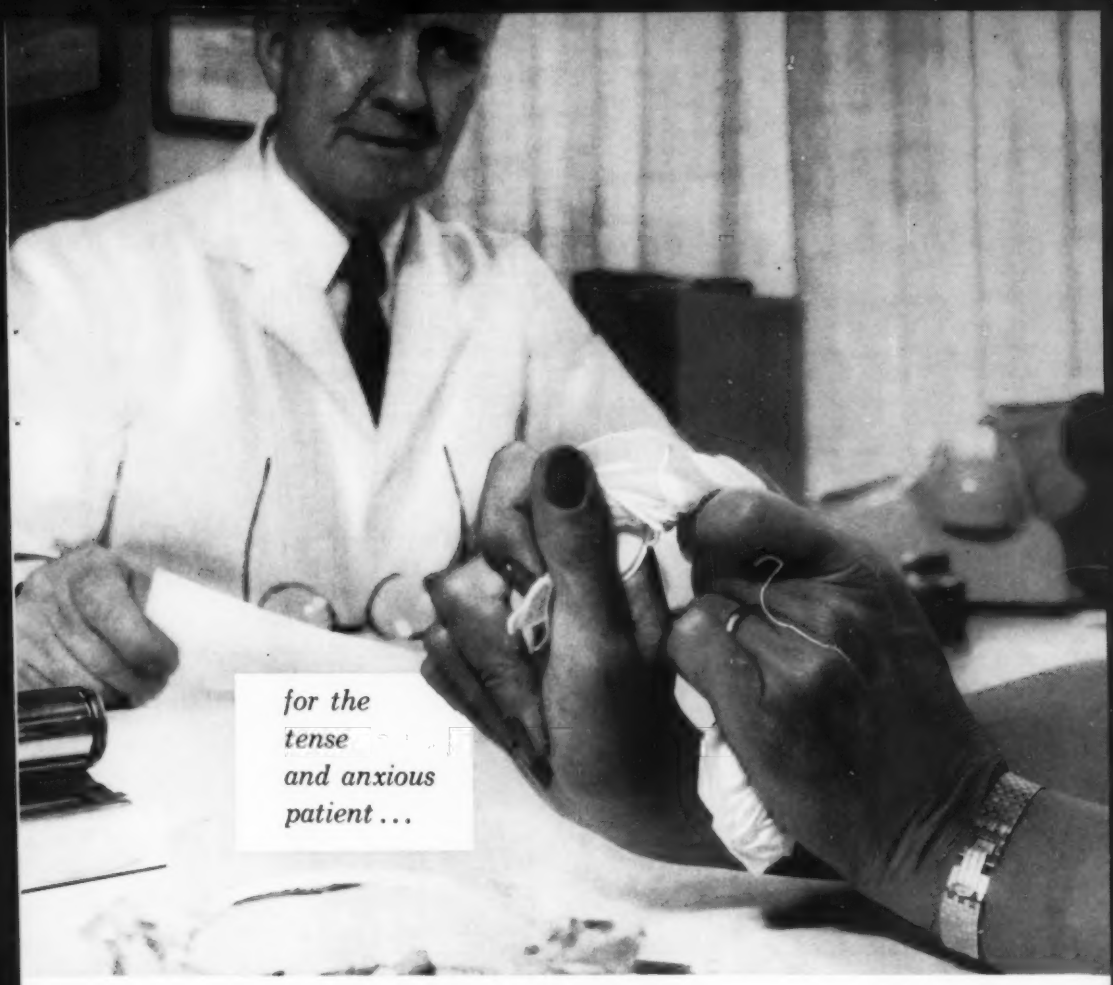
PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

BENADRYL®

antihistaminic-antispasmodic

cuts most allergens down to size!



the only sustained-release tranquilizer that does not cause autonomic side reactions

- SAFE, CONTINUOUS RELIEF of anxiety and tension for 12 hours with just one capsule—without causing autonomic side reactions and without impairing mental acuity, motor control or normal behavior.
- ECONOMICAL for the patient—daily cost is only a dime or so more than for barbiturates.

Meprospan®-400

400 mg. meprobamate (Miltown®) sustained-release capsules

Usual dosage: One capsule at breakfast lasts all day; one capsule with evening meal lasts all night.

Available: *Meprospan-400*, each blue-topped capsule contains 400 mg. Miltown (meprobamate). *Meprospan-200*, each yellow-topped capsule contains 200 mg. Miltown (meprobamate). Both potencies in bottles of 30.

WALLACE LABORATORIES / *Cranbury, N. J.*

CME-4232

900 CALORIES AND NO DOCTOR?

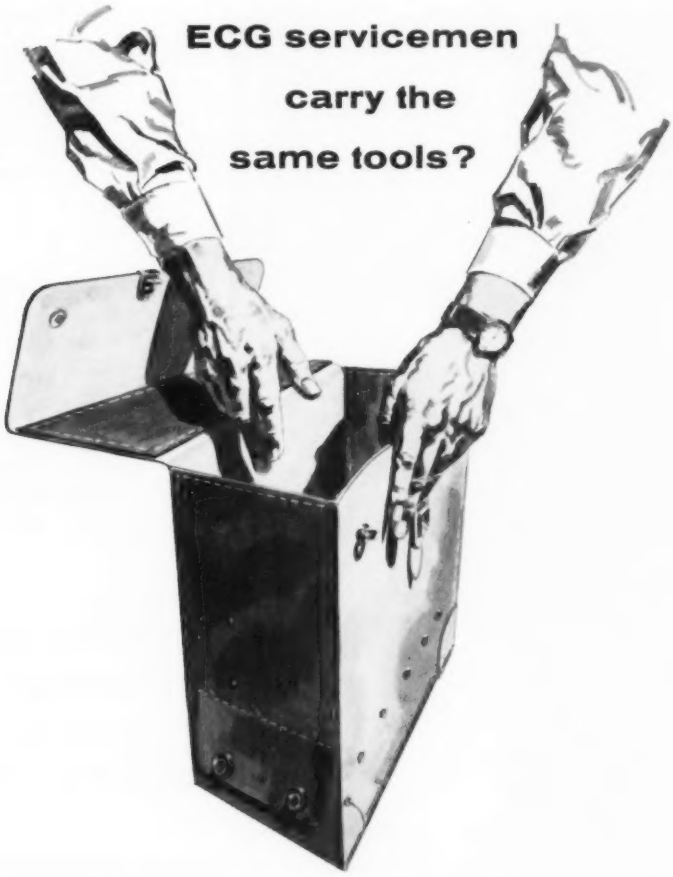
LET'S CONSIDER . . . *A 900 calorie daily diet that supplies no bulk is frequently not enough* to even dent the appetite and "bulk hunger" demands of many overweight patients. Neither is a self-administered diet plan a suitable substitute for a *medically-supervised* weight reduction program. Such fad-inspired regimens overlook the fundamental physiologic problems of obesity. Obocell helps the obese patient adhere to *your* diet chart by curbing gnawing appetite *and* suppressing bulk hunger during and between meals. Under your care, and with Obocell as the basic control factor, patients can arrive at their desired weight on schedule. Time and again, this combination of a *physician-prescribed* diet reinforced by Obocell therapy has proved to be the safest, most satisfactory way to shorten patients' beltlines while lengthening their lifelines. **IRWIN, NEISLER & CO.** DECATUR, ILL.

***only* through your prescription**

OBOCELL® TABLETS

OBOCELL®, brand of anorexic, Neisler. **Formula:** Dextro-Amphetamine Phosphate, 5 mg.; Nicel (Irwin, Neisler's brand of high-viscosity Methylcellulose), 160 mg. **Action:** Obocell controls the appetite by acting on the central nervous system, and controls bulk hunger by supplying non-nutritive bulk to create a sense of fullness and satisfaction. **Dosage:** 3 to 6 tablets daily with a full glass of water, preferably one hour before meals.

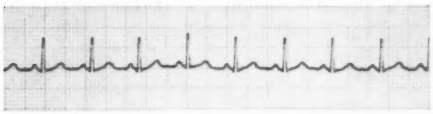
do all ECG servicemen carry the same tools?



Perhaps they do . . . if you consider their "tools" to be only soldering irons, spare components, milliammeters and the like. But what about their training, experience, and personal interest in your satisfaction?

The men who service Sanborn electrocardiographs are qualified technicians — highly skilled and experienced in medical electronics. Their training and experience are important; but important, too, is their direct, personal interest in providing every Sanborn owner with competent, prompt, responsible service.

It's a "service tool" well worth remembering the next time you buy an electrocardiograph.

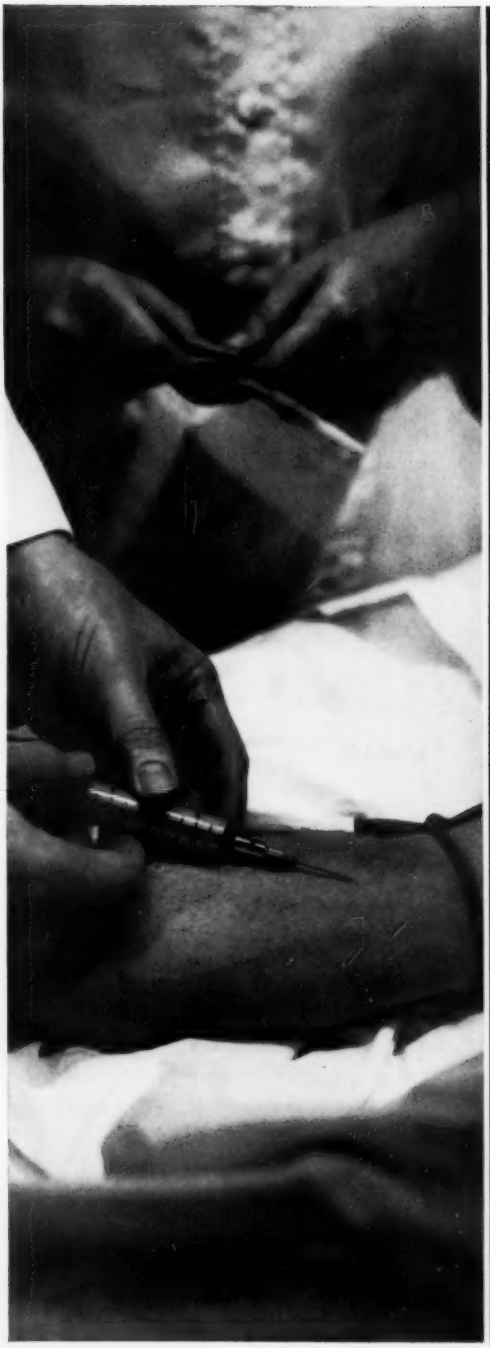


MEDICAL DIVISION

SANBORN COMPANY

175 Wyman St., Waltham 54, Massachusetts

NEW YORK *Branch Office* 1841 Broadway, Circle 7-5794 and 7-5795



Lilly

QUALITY / RESEARCH / INTEGRITY

■ *Staphylococcus resistance to Vancocin has not been a clinical problem*

an important solution in the management of resistant staphylococcus infections

VANCOCIN®

(vancomycin, Lilly)

Vancocin is bactericidal in readily achieved serum concentrations.

Vancocin is effective against antibiotic-resistant gram-positive pathogens. Cross-resistance does not occur.

Vancocin averts the development of antibiotic-resistant organisms.

Supplied:

Only as Vancocin, I.V., 500 mg., in 10-cc. rubber-stoppered ampoules. Before administration, the physician should consult essential information contained in the package.

110113

SECOND SERIES JUNE 1961 VOL. 37, NO. 6

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

Pyelonephritis 367
Edward A. Gall

Relative Importance of Late Sequelae of Irradiation in Man 383
R. R. Newell

Common Urological Problems in General Practice . . 411

Transcription of a Panel Meeting on Therapeutics
Victor F. Marshall, Simon A. Beisler, Frank C. Hamm and Ralph J. Veenema

The Place of Lumbar Sympathectomy in the Light of Recent Advances in Vascular Surgery 433
Ferdinand F. McAllister

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

Annual subscription United States and Canada $8.00. All other countries $9.00. Single copies 90c.
ADVERTISING OFFICE • 30 ROCKEFELLER PLAZA, N. Y. C. 20 • CIrcle 7-7706
Copyright 1961 by The New York Academy of Medicine

OFFICERS AND STAFF OF THE ACADEMY – 1961

FRANK GLENN, *President*

Vice-Presidents

G. JARVIS COFFIN — M. RALPH KAUFMAN — RUSTIN MCINTOSH

SHEPARD KRECH, *Treasurer*

FREDERICK H. WILKE, *Recording Secretary*

Trustees

STUART L. CRAIG
*FRANK GLENN
HAROLD BROWN KEYES
*SHEPARD KRECH
SAMUEL W. LAMBERT, JR.
ROBERT L. LEVY
ASA L. LINCOLN
JOHN L. MADDEN
WILLIAM BARCLAY PARSONS
JEROME P. WEBSTER
ORRIN S. WIGHTMAN
*FREDERICK H. WILKE
ROBERT H. WYLIE

Council

The President — The Vice-Presidents — The Trustees
The Treasurer — The Recording Secretary

The Chairmen of Standing Committees:

CARL T. NELSON, *Admission*
MILTON J. GOODFRIEND, *Public Health*
ARTHUR M. MASTER, *Special Studies*
BRONSON RAY, *Library*
JAMES E. MCCORMACK, *Medical Education*
G. JARVIS COFFIN, *Sections*

HOWARD REID CRAIG, *Director*

GERTRUDE L. ANNAN, *Librarian*

HARRY D. KRUSE, EXECUTIVE SECRETARY, *Committee on Public Health*

AIMS C. MCGUINNESS, EXECUTIVE SECRETARY, *Committee on Medical Education*

IAGO GALDSTON, EXECUTIVE SECRETARY, *Committee on Special Studies*

ROBERT L. CRAIG, EXECUTIVE SECRETARY,
Committee on Publications and Medical Information

ROBERT M. BRERETON, *Business Manager*

DAVIS POLK WARDWELL SUNDERLAND & KIENDL, *Legal Counsel*

Library Consultants

JANET DOE — CURT PROSKAUER

EDITORIAL BOARD

CHARLES E. KOSSMANN, *Chairman*
GERTRUDE L. ANNAN
MARGARET BEVANS
RALPH W. GAUSE
CHARLES A. RAGAN, JR.
ROBERT L. CRAIG,
Secretary and Editor

---

* Ex Officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 37, NO. 6 JUNE 1961

PYELONEPHRITIS*

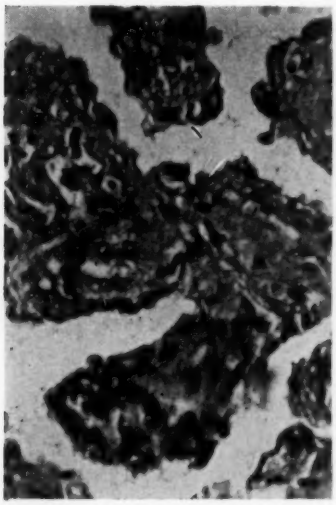
EDWARD A. GALL

Mary M. Emery Professor of Pathology, University of Cincinnati College of Medicine, Cincinnati, Ohio

A MALADY which occurs with high incidence in a necropsy population but is recognized in life in only a fraction of cases deserves serious exploration. Pyelonephritis is such an ailment—and its inclusion upon this program would indicate a recognition of its importance. I had expected that my purpose here was to set the stage in a preliminary manner for a more skilled individual who could better bring life to the subject. Since this is not to be—at least, at the moment—I propose to comb through the information available (my own experience included), garb it in respectable fashion, and re-introduce it to your tender mercies.

Pyelonephritis was for a long period considered apart from the category of "medical" nephritis and thought to be of interest only to those dealing with urologic disturbances.[1, 2] It lay in the group of infectious complications attending urinary tract obstruction; i.e., prostatic enlargement, genito-urinary neoplasm, calculous disease, stricture and disorders of innervation.[3] "Ascending infection" was the catch-phrase; the urologist, the accountable physician.[4, 5] It was casually conceived that retained urine constituted an endogenous culture medium and a

* Presented at the Fourth Annual Postgraduate Week, *Frontiers in Medicine and Surgery*, of The New York Academy of Medicine, October 27, 1960.



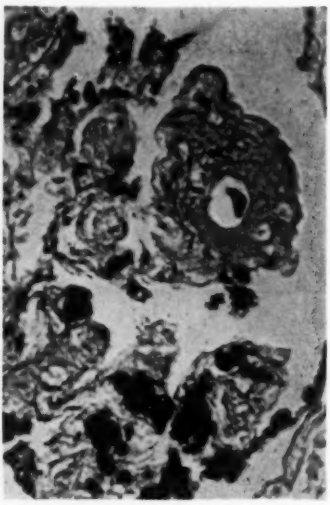


Figure 1—Top Left—Subacute Lobular Glomerulonephritis (Guy's Hospital Museum #1605). A portion of glomerulus is the seat of increased cellularity, lobular digitation and reduction of its capillary bed. Elsewhere in the section (not shown in the photograph) there is crescent formation. Hematoxylin and eosin stain, X 350.

Figure 2—Top Right—Renal Amyloidosis (Guy's Hospital Museum #1606). A thick hyaline deposit surrounds widened glomerular capillaries. Formalin pigment causes heavy granular artifact. Methyl violet stain, X 300.

Figure 3—Lower Left—Intercapillary Glomerulosclerosis, diabetic nephropathy (Guy's Hospital Museum Specimen #1611). Glomerular tufts are thrown into prominence by spherical nodules of hyalin. The latter are framed by arched glomerular capillaries. Hematoxylin and eosin stain, X 160.

pathway for the ascent of bacteria. Dynamic factors imposed excretory impairment; bacterial intrusion represented an incidental but, nonetheless, serious complication. There is no denial that this does indeed represent one mechanism of pyelonephritis, but it has become clearly evident that it is by no means the only one.

Bright's remarkable observations have served for more than a century as a baseline for the correlation of clinical manifestations with renal alteration. The pattern of azotemia, hypertension, pallor, fluctuating edema and related features were long taken to reflect primary renal incapacity, and were ultimately regarded as indications of glomerulonephritis. Advancing knowledge, however, has led to the appreciation that more than one condition prevails in the cases seemingly supporting this concept.[6-8] A re-examination of three of Bright's specimens, poorly preserved over the hundred-year interval, shows them to be lobular glomerulonephritis (Figure 1), renal amyloidosis (Figure 2) and diabetic glomerulopathy (intercapillary glomerulosclerosis) (Figure 3). Undoubtedly there are many other variations. It is apparent that the clinical complex may well derive from a miscellaneity of different lesions.

Long ago, this became apparent with respect to nonglomerular lesions when experience dictated that at least one other commonplace process might evoke identical symptomatology. From many sources, accumulated evidence attested to the existence of hypertension without detectable vascular alteration,[9, 10] the ultimate vulnerability of the renal arterial system to blood pressure elevation, a progressive renal impairment by reason of ischemic factors and, finally, the full spectrum of chronic uremia.[11] Bright's disease, then, might be a reflection of two very different conditions, each progressing to a similar end-point of functional derangement. The one, glomerulonephritis, was considered by many to be common;[8] the other, vascular nephritis or arteriolonephrosclerosis, a comparatively infrequent offender. Neither the pathogenetic nor the overt ramifications of these two conditions require elaboration here. It should be emphasized, however, that in their advanced, cicatrized stages, a distinction between the two is often difficult not only by clinical criteria but pathologically as well.[12]

Although heralded by sporadic reports that scarred, contracted kidneys and accompanying evidences of renal failure might also result from bacterial infection,[13-15] it was not until the mid-1930's that Long-

cope[5, 16] and Weiss and Parker[2, 11, 17] brought chronic pyelonephritis into proper perspective. It is difficult, in view of the importance this disease has achieved, to appreciate that until two decades ago few students of renal disorder, and still fewer writers of textbooks, gave more than passing reference to it as a major problem in non-obstructive chronic renal failure.

A definition of pyelonephritis is hard to devise, probably because it appears in so many different forms. Incorporated in its scope is "pyelitis", once considered a potential precursor; now known to be a concomitant.[18-20] In broadest terms, the disorder may be considered an inflammation of kidney substance initiated by direct bacterial action. Perhaps the process may be better defined by enumerating its characteristics and discussing the mechanisms of its development.

Clinico-Pathologic Features

The kidney with pyelonephritis appears at its inception as a swollen, inflamed organ flecked with minute purulent foci.[3, 6] The renal pelvis may or may not be dilated, but its mucosa is furry, with congestion and edema.[21] Microabscess formation and diffuse interstitial suppuration are accompanied on the one hand by destruction of pus-filled capillary channels, and on the other by intratubular accumulations of neutrophils, bacteria and detritus. In some instances, the process has apparent vascular origin;[22] in others, the tubule serves as a nidus.[1, 23, 24] The urine is cloudy and the patient suffers not at all or has back pain, frequency, dysuria, fever and attendant disabilities.[4] In the circumstance of urinary tract obstruction, this may dominate the clinical course.[1, 25] With correction of the obstruction, or in its absence, by suitable therapy or even spontaneously, regression of the exudate is the rule.[18] In parallel, there is subsidence of those clinical manifestations which may have been overt. Resolution, however, is rarely complete, and a varying degree of focal parenchymal scarification remains. This is ordinarily of functionally negligible significance, but the initial lesion may on occasion be sufficiently severe to result in progressive parenchymal destruction. This is the case in instances of massive pyonephrosis or in the face of necrotizing papillitis, both of which represent extreme variants of acute pyelonephritis.[26, 27] In the usual circumstance, each insignificant scar dividing or deforming a nephron results in its atrophy. In the event of repetitious episodes, major impairment of total function may

Fig. 4a

Fig. 4b

Figure 4a—Chronic pyelonephritis. The renal capsule has been stripped. The diffuse, fine, surface nodularity is interrupted by shallow, crater-like depressions indicating focal atrophy of underlying parenchyma.

Figure 4b—Chronic pyelonephritis. The sectioned kidney shows an abundance of peripelvic fat, irregular cortical narrowing and loss of corticomedullary distinction. In silhouette, a shallow, U-shaped concavity reflects focal cortical scarring.

be anticipated. More important, however, each minor scar appears to facilitate subsequent trapping of bacteria in the course of minor incidents of infection—thus increasing the vulnerability of the organ to continuing disintegration.[25]

Serial attacks may not affect each kidney simultaneously or with equal intensity. The end product, therefore, is often asymmetrical as to distribution of lesions and size of organs.[28-31] In occasional instances the infection is one-sided only; the contralateral kidney may show few or no lesions. This is the case if the uropathy stems from unilateral obstruction.

In the main, the kidney with advanced pyelonephritis is shrunken, its diffusely pebbled surface interrupted by spottily distributed, shallow, concave depressions[3, 4] (Figure 4). The cortex is narrow and blends indistinguishably with the medullary component; dirty fluid is evacuated from scattered cystic excavations. Peripelvic fat is unduly abun-

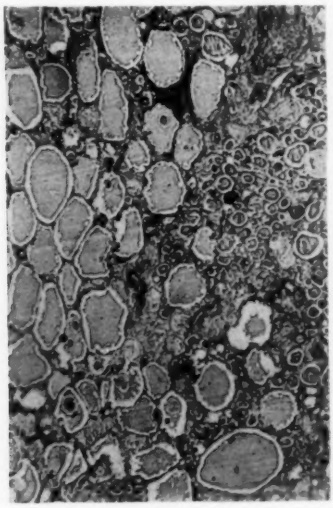


Fig. 5

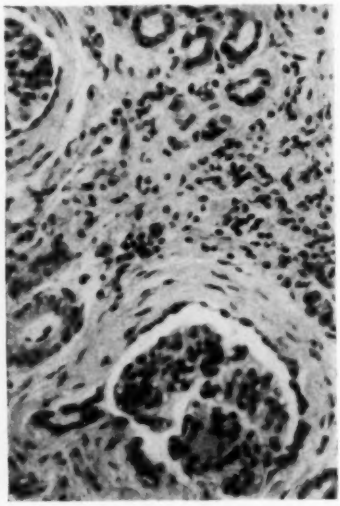


Fig. 6

Figure 5—Chronic pyelonephritis: "thyroidization". Collecting tubules are dilated and filled with a homogenous eosinophilic precipitate. Epithelium is flattened. There is obvious resemblance to thyroid gland. Hematoxylin and eosin stain, X 40.

Figure 6—Chronic pyelonephritis. Interstitial lymphocytic infiltration, fibrosis and tubular atrophy prevail. Glomeruli, though comparatively intact, are embraced by thick, laminated collars of periglomerular fibrosis. Hematoxylin and eosin stain, X 160.

dant. The pelvis, though fibrotic and thick-walled, is disproportionately enlarged. This represents either frank distention by obstruction or a failure to contract in proportion to the shrinking kidney. Highlighting the microscopic appearance are the varied features of atrophy, fibrosis and accompanying inflammatory phenomena. The latter may appear as extensive lymphocytic and plasma cell infiltrations, focal suppuration in or beside tubules, or as minor degrees of residual inflammation only. Some glomeruli appear undisturbed; others exhibit tuftal adhesions, intercapillary sclerosis or total hyalinization.[21, 32] Contributing to glomerular strangulation is a characteristic concentric laminated fibrosis embracing Bowman's capsule.[2, 22, 24] This may be a residuum of earlier inflammation or reflect, as some have claimed, occlusion of periglomerular lymphatics. Although reduced markedly in number, tubules which do persist are in varying states of atrophy and disintegration. Some

of this exists by reason of glomerular obliteration, some because of the direct effects of bacterial invasion. Many large groups of tubules containing homogeneous eosinophilic, colloid-like substance have undergone cystic dilatation and afford to the area an appearance akin to that of the involuted thyroid gland.[6, 12, 24] "Thyroidization" of tubules (Figure 5) and concentric periglomerular fibrosis (Figure 6) have been considered by many to be pathognomonic of pyelonephritis.[2, 6, 24]

Sharing the progressive parenchymal alteration, intrarenal vessels undergo thickening and sclerosis. By some, this is considered a reaction to parenchymal atrophy;[3] by others, the direct result of inflammation and healing.[8, 18, 32] Whatever the manner, arteriolar mural thickening and lumen narrowing are regularly manifest. Nor do they necessarily indicate the existence of systemic hypertension.[10, 34-36]

There is little problem, ordinarily, in distinguishing the various types of renal disease pathologically. In a few, the degree of alteration is of such order, however, that this proves to be difficult. Of particular interest, in this connection, is the existence in all forms of chronic kidney diseases—of morphologic features considered peculiar to pyelonephritis.[2, 37] It is as though this lesion superimposes itself, much as in the case of arteriolar sclerosis, upon most or all of the other forms of renal disorders, i.e., chronic glomerulonephritis, nephrosclerosis, diabetic nephropathy, congenital polycystic renal disease, etc.[5, 36] In some, the features of pyelonephritis are of minor extent. In many, however, the degree of involvement is of such order that determination of the underlying primary disease is governed by recognition of subtle histologic characteristics, and occasionally is made by arbitrary decision alone. It is obvious, therefore, that the actual incidence of pyelonephritis far exceeds that indicated by the separation of cases on the basis of primary disorder alone.

Incidence

During the five-year period, 1954-1959, 2,991 adults were examined at necropsy at the Cincinnati General Hospital. Among these, major renal lesions were encountered in one third (Table I). The bulk of the pathologic alterations were of long standing (915 of 997 cases); renal insufficiency had supervened in only 39 per cent (Table II), an incidence of 12 per cent in the over-all population sample studied. Pertinent to the present discussion, the largest single group among those

TABLE I—RENAL DISORDERS AT NECROPSY
(Cincinnati General Hospital—1954-9)*

Nephrosclerosis	362	Toxic nephrosis	17
Pyelonephritis	360	Necrotizing papillitis	13
Glomerulonephritis	74	Polycystic disease	10
Diabetic nephropathy	65	Infarct(ion)	16
Tubulorhexis	33	Miscellaneous**	28
Cortical necrosis	19		
		Total	997

* Adults only—2,991
** Myeloma, amyloid, lupus erythematosus, gout, etc.

TABLE II—CHRONIC UREMIA AT NECROPSY
(Cincinnati General Hospital; 2,991 Adults)

	*No. of Cases**	*Uremia*
Nephrosclerosis	362	23%
Pyelonephritis	360	49%
Glomerulonephritis	74	47%
Diabetic nephropathy	65	43%
Infarct(ion)	16	50%
Polycystic disease	10	78%
Miscellaneous	28	79%
Total	915	39%

* All cases with and without uremia.

with uremia (51 per cent) were examples of pyelonephritis (Table III). These were, in actuality, twice as numerous as cases of arteriolonephrosclerosis with uremia (of which more than half were examples of malignant hypertension), and five times more abundant than cases of glomerulonephritis.

More than half of the cases of pyelonephritis (54 per cent) were associated with lower urinary tract obstruction (Table IV). Uremia, as might be anticipated, was more common than in the nonobstructive group, since obstruction alone could well induce azotemia without significant inflammatory alterations of the kidney. In the series analyzed, however, intrarenal lesions were of equal severity in both groups.

TABLE III—CHRONIC UREMIA
(915 Cases)

	Per Cent of Total
Pyelonephritis, obstructive	27%
Pyelonephritis, nonobstructive	24%
Nephrosclerosis, benign	10%
Nephrosclerosis, accelerated	13%
Glomerulonephritis	10%
Diabetic nephropathy	8%
Polycystic disease	2%
Miscellaneous	6%
Total with Uremia	100%

TABLE IV—UREMIA-PYELONEPHRITIS
(175 Cases)

	No. of Cases	*Per Cent*
Obstructive	94	54
Nonobstructive	81	46

Many have claimed pyelonephritis to be the most frequent form of renal disease.[4, 18, 38, 39] This is assuredly the case if the primary and secondary varieties are combined. Moreover, it often appears that the development of the pyelonephritic component constitutes the factor precipitating failure of a kidney only partially impaired by another disorder.

PATHOGENESIS

As indicated at the outset, until relatively recently the mode of induction of pyelonephritis was believed to be through the medium of lower urinary tract obstruction of one or another form.[1, 3, 5] Implicit in the process was an impairment of uretero-vesical sphincteric efficiency.[25] Urinary stasis was considered, in turn, a likely milieu for the engraftment of microorganisms often with low virulence. Sources of inoculation were thought to be the obstructing lesions themselves, undergoing or causing tissue necrosis, the introduction of bacteria via the

urethra by instrumentation or manipulation, or the extension of organisms from the lymphatics of neighboring structures, notably the intestine.[25] The bacteria, having been introduced, were thought to rise by intrinsic motility, diffusion, or ureteral reflux through the column of urine to attack the renal pelvis and, secondarily, the parenchyma.[40] The kidney, its susceptibility enhanced by restricted secretion, might then be expected to undergo the gamut of pyelonephritic alterations subject to interruption or reactivation at any stage. Some suggested the progressive upward passage of infection by direct extension along succeeding segments (cystitis–ureteritis–pyelitis–pyelonephritis); and others an ascent of bacteria by periureteral lymphatic channels. Most authorities have conceded the existence of an ascending intra-ureteral route, although emphasis upon this mechanism has lessened in recent years.

Having widest support at the present time is the concept of descending infection with a hematogenous source for infective agents.[24, 31, 41] It is considered that these organisms, naturally inhabiting the blood stream or introduced into it by infections elsewhere in the body, course through the renal circulation and excretory elements in a periodic manner. Influenced by a number of different factors, the passage of the bacteria may be intercepted at some point in the kidney and then proceed to induce focal inflammation.

There is much experimental evidence in support of this concept. For example, it has been noted that transitory bacilluria may be induced by the introduction of coliform organisms intravenously, but that neither lesions nor bacilli are detectable in the kidney after a comparatively brief period of hours.[42] On the other hand, if this is carried out in the face of temporary obstruction of a ureter,[13] or following manipulation of the kidney through the intact abdominal wall,[43-44] or if virulent staphylococci are introduced without ureteral obstruction,[28, 42] suppurative renal lesions ensue. These, moreover, though ultimately healed, leave permanent cicatricial stigmata. Thereafter, the introduction of colon bacilli, now without the factor of ureteral obstruction, result in the seeding of the kidney by microabscesses and the development of a progressive lesion. Animals which survive such procedures for a period of months exhibit lesions identical with those encountered in advanced human pyelonephritis.[41, 42]

It is reasonable to assume that, in the human subject, random passage of bacteria through the kidney in the face of urinary tract obstruc-

tion might easily follow the same sequence of events. Pyelonephritis may, therefore, represent a hematogenous infection whether or not obstruction is present. The existence of urinary tract obstruction is not a requisite, but constitutes an added predisposing hazard. Indeed, the causative organism may actually stem from the lower urinary passages themselves, to reach the kidney by way of the blood stream as well as by the ascending route.

Perhaps, in this series of experimental observations and clinical inferences, there lies an explanation for the frequent concomitance of pyelonephritis-like alterations in other forms of renal disease. The kidney, which is the seat of glomerulonephritis, cystic disease, nephrosclerosis, amyloidosis or some other process is, in essence, an organ receptive to many forms of intercurrent infection.[12, 20, 28] Pyelonephritis as a complicating disease should actually be anticipated as the rule, and not as a puzzling exception.

A third possible pathogenetic hypothesis is supported, at the moment, by little more than speculation. It is conceivable that renal tissue, once damaged by any means, may provide a substance altered in such a way as to be foreign to the host economy and thus initiate a state of auto-immunization.[45] By this means, progressive damage may be the result of selfinduced antibody action in the absence of recurrent infection. This is a hypothesis currently popular in other areas. A number of experimental approaches have indicated the potentiality for auto-antibody production in many different viscera.[46] This mechanism has, in turn, been invoked in explanation of several human diseases of obscure etiology. Chronic thyroiditis[47] and sympathetic ophthalmia[48] are two in point.

The possibility of such a relationship in both primary and secondary pyelonephritis deserves at least casual consideration. One need only have in mind the lesions which appear in kidneys serving as homotransplants to recognize this possibility.[49] In both the experimental animal and in the few human examples of renal transplant which have survived for a reasonable interval, the rejection pattern has much similarity to many of the tissue changes in pyelonephritis. Such a phenomenon would bear no relationship to acute pyelonephritis, where infection appears to be an obvious cause. On the other hand, auto-immunization as an explanation for the progression of pyelonephritis, once the acute episode has subsided, appears to be a reasonable probability. Tissue damaged by

noninfectious means may also serve as an antigenic source; hence the appearance of pyelonephritis-like interstitial inflammation and fibrosis as secondary alterations in other forms of renal disease.

Discussion

The frequency with which pyelonephritis is encountered as an incidental feature at necropsy can in no way minimize its importance as a lethal process.[4, 7, 13, 16] It constitutes the primary lesion in more than one half of the cases succumbing to chronic renal insufficiency (Table III). In how many others its insinuation as a complication trips the fatal balance can only be surmised. Even a cursory survey will reveal a surprising coincidence of occurrence with all other forms of chronic noninfectious renal disorder.

In many instances the early stages, and even more often the succeeding phases of progression, fail to attain clinical recognition. Pyelonephritis accompanying obstructive uropathy may be completely obscured by the evidences of lower urinary tract abnormality.[39, 50] Even among these, however, both the obstructing process and the renal infection may escape notice. This is particularly the case in aberrations of innervation (spina bifida, syringomyelia) and in benign obtrusions (stricture, prostatic hypertrophy). In a significant number, the renal lesion is manifested only by nonspecific evidences of systemic infection with fever, prostration and sepsis.[51] Telltale pyuria and bacilluria, dysuria and flank or lumbar pain when encountered, of course, are helpful signs. In almost all the patients with the nonobstructive form of the disease (pyelonephritis lenta),[37] the continuing course of many years' duration is generally without detectable features. Those unfortunate individuals who eventually attain the ultimate in renal impairment evince hypertension and the uremic syndrome, and are indistinguishable from patients with any of the other forms of Bright's disease. Save in the group with extrarenal obstructing lesions, which should be detected more readily, the knowledge that pyelonephritis constitutes the most common of crippling renal diseases provides a basis for tentative clinical recognition.

The demonstration of pyuria or bacteriuria by examination of voided samples is manifestly a useful diagnostic measure.[22, 52] But bacilluria is no certain indication of infection, and pyuria may simply reflect infrarenal urinary tract inflammation.[6] Pyemia and its related clinically

TABLE V—CONTRACTED KIDNEYS*
(2,991 adults, necropsy)

	Bilateral		*Unilateral*	
	No. of Cases	*Uremia*	*No. of Cases*	*Uremia*
Nephrosclerosis	33	6%	15	0
Pyelonephritis	28	60%	39	49%
Glomerulonephritis	3	67%	1	100%
Miscellaneous**	0	—	17	24%
Total	64	34%	72	33%

* Bilateral, 150 gm.; unilateral, 75 gm.
** Vascular occlusion, infarction, hypoplasia, atrophy.

manifest focal lesions may indicate a renal flareup of suppurative character;[22, 25] the catastrophic manifestations of necrotizing papillitis, particularly in the diabetic, are useful hallmarks.[27, 53] Curious metabolic phenomena attributable to loss of sodium[54] or potassium[51] are particularly suggestive of pyelonephritis, and are said to be rare in other renal disorders. Acidosis, evidences of calcium and phosphorus imbalance, anemia, azotemia, hypertension, pericarditis—these seemingly occur in all forms of prolonged renal failure and do not serve in distinguishing one from the other.[4, 7, 22] It is claimed by some that heart failure, coronary insufficiency and cerebral hemorrhage are relatively uncommon with the hypertension accompanying pyelonephritis, but these negative observations are of doubtful value.[2]

Subdivision into obstructive and nonobstructive pyelonephritis has no invariable clinical correlative significance. Manifestations do not regularly pattern themselves in parallel with the anatomic process. Moreover, except in flagrant examples of obstruction, intrinsic renal lesions do not have special characteristics. Classification by pathologic stage of activity has some value in formulating a working knowledge of pathogenesis. The terms acute, chronic active, healed, and chronic or healed with reactivation are self-explanatory qualifying expressions.[11, 17]

The severely shrunken kidney (less than 75 grams) is a stigma of pyelonephritis in many instances. This is particularly so in the unilateral lesion, in which 39 of 72 examples (54 per cent) proved to be of this nature (Table V). Less often the case with the bilaterally shrunken kidneys, this is nonetheless a frequent indication (44 per cent) of pyelo-

nephritis. It is certainly not the case, however, that the smallest kidneys usually represent glomerulonephritis;[5, 13, 31, 34] in our experience chronic pyelonephritis prevails in the majority of such cases.

The superimposition of pyelonephritis upon pre-existing renal disease of other varieties deserves repeated emphasis. This may be taken to indicate the increased susceptibility of scarred organs to blood-borne infection. On the other hand, it may equally well be a reflection of the sensitization of the host to a damaged viscus; the inflammatory process thus may represent an auto-immune rejection phenomenon.

It is probable that pyelonephritis as a primary disease is induced by microorganisms entering by the renal vascular system. Organisms with relative necrotizing capacity (staphylococcus) may establish permanent lesions without potentiating obstruction. Once having done so, the affected kidney is thereafter susceptible to less virulent bacteria (Escherichia), and progression may be caused by repeated seedings. Initial establishment of the lesion by nonvirulent coliform bacilli requires such other factors as urinary obstruction or a previously scarred parenchyma.

Summary

1. Pyelonephritis is a renal disorder with many facets, triggered at its outset by bacterial infection.

2. Obstructive uropathy may be an important contributory, but not a requisite, factor.

3. Infection stems from the blood stream in almost all instances; once begun, however, initial infections are prone to heal with variable degrees of scarring.

4. Kidneys so affected are functionally adequate but, along with those altered by noninfectious diseases, have a heightened susceptibility to minor re-infections (or, conceivably, to damage by auto-immune mechanisms).

5. Ultimately, progressive functional impairment may lead to a pattern of chronic renal insufficiency identical with that encountered in other forms of Bright's disease.

REFERENCES

1. Lieberthal, F. Pyelonephritic contracture of the kidney, *Surg. Gynec. Obstet. 69:* 159-71, 1939.

2. Weiss, S. and Parker, F., Jr. Vascular changes in pyelonephritis and their relation to arterial hypertension, *Trans. Assoc. Amer. Phycns. 53:*60-73, 1938.

3. Bell, E. T. Exudative interstitial ne-

phritis (pyelonephritis), *Surgery 11:* 261-80, 1942.

4. Allen, A. C. *The Kidney. Medical and Surgical Diseases.* New York, Grune and Stratton, 1951, 583 pp.
5. Longcope, W. T. and Winkenwerder, W. L. Clinical features of the contracted kidney due to pyelonephritis. *Bull. Johns Hopk. Hosp. 53:*255-87, 1933.
6. Boyd, W. Changing concepts of pyelonephritis, *Canad. med. Assoc. J. 47:* 128-33, 1942.
7. Likely, D. S., Lisa, J. R. and Solomon, C. Pyelonephritis with death in uremia. *J. Amer. med. Assoc. 119:*397-400, 1942.
8. Mansfield, J. S., Mallory, G. K. and Ellis, L. B. Differential diagnosis of chronic Bright's Disease. A clinicopathological correlation, *New Engl. J. Med. 229:*387-95, 1943.
9. Castleman, B. and Smithwick, R. H. Relation of vascular disease to the hypertensive state, based on a study of renal biopsies from 100 hypertensive patients, *J. Amer. med. Assoc. 121:*1256-61, 1943.
10. Taylor, H. E. Pathogenesis of chronic atrophic pyelonephritis and its possible relation to the production of hypertension, *Canad. Med. Assoc. J. 47:*24-27, 1942.
11. Weiss, S. and Parker, F., Jr. Pyelonephritis: its relation to vascular lesions and to arterial hypertension, *Medicine 18:*221-315, 1939.
12. Kincaid-Smith, P. Vascular obstruction in chronic pyelonephritic kidneys and its relation to hypertension, *Lancet 2:*1263-68, 1955.
13. Birchall, R. and Alexander, J. E. Medical aspects of pyelonephritis, *Medicine 29:*1-28, 1950.
14. Löhlein, M. Ueber Schrumpfnieren, *Beitr. path. Anat. 63:*570-632, 1917.
15. Staemmler, M. and Dopheide, W. Die pyelonephritische Schrumpfniere. *Virchows Arch. 277:*713-56, 1930.
16. Longcope, W. T. Chronic bilateral pyelonephritis: its origin and its association with hypertension, *Ann. intern. Med. 11:* 149-63, 1937-8.
17. Weiss, S. and Parker, F., Jr. Relation of pyelonephritis and other urinary-tract infections to arterial hypertension, *New Engl. J. Med. 223:*959-67, 1940.
18. Brainard, H. D. and Cecil, L. M. Observations on the pathogenesis, course and treatment of non-obstructive pyelonephritis, *Ann. intern. Med. 45:*232-41, 1956.
19. Griffin, M. A. Pyelonephritis in infancy and childhood: its bacteriology and pathology, *Arch. Dis. Childh. 9:*105-14, 1934.
20. Marshall, A. G. Persistence of foetal structures in pyelonephritic kidneys, *Brit. J. Surg. 41:*38-50, 1953.
21. Putschar, W. G. J. Some aspects of the pathology of pyelonephritis, *J. Urol. 43:* 793-803, 1940.
22. Fitzgerald, P. J. Pyelonephritis: its newer concept and clinical significance with a review of the literature, *U.S. Nav. med. Bull. 45:*108-25, 1945.
23. Crabtree, E. G. and Prien, E. L. Nature of renal injury in acute and chronic colon bacillus pyelonephritis in relation to hypertension: combined clinical and pathological study, *J. Urol. 42:*982-95, 1939.
24. Mallory, G. K., Crane, A. R. and Edwards, J. E. Pathology of acute and healed experimental pyelonephritis, *Arch. Path. 30:*330-47, 1940.
25. Beeson, P. B. Factors in the pathogenesis of pyelonephritis, *Yale J. Biol. Med. 28:*81-104, 1955.
26. Edmondson, H. A., Martin, H. E. and Evans, N. Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus, *Arch. Intern. Med. 79:*148-75, 1947.
27. Mandel, E. E. Renal medullary necrosis, *Amer. J. Med. 13:*322-27, 1952.
28. DeNavasquez, S. Pathological aspects of chronic pyelonephritis, *Proc. roy. Soc. Med. 47:*629-31, 1954.
29. Emmett, J. L., Alvarez-Ierena, J. J. and McDonald, J. R. Atrophic pyelonephritis versus congenital renal hypoplasia, *J. Amer. med. Assoc. 148:*1470-77, 1952.
30. Platt, R. and Davson, J. Clinical and pathological study of renal disease; Part II. Diseases other than nephritis, *Quart. J. Med. 19:*33-55, 1950.

31. Rosenheim, M. L. Discussion on chronic pyelonephritis, *Proc. roy. Soc. Med. 47:* 628-29, 1954.
32. Kimmelstiel, P. and Wilson, C. Inflammatory lesions in the glomeruli in pyelonephritis in relation to hypertension and renal insufficiency, *Amer. J. Path. 12:* 99-106, 1936.
33. Kimmel, G. C. Hypertension and pyelonephritis in children, *Amer. J. Dis. Child. 63:*60-75, 1942.
34. Barker, N. W. and Walters, W. Hypertension and chronic atrophic pyelonephritis. Results of nephrectomy, *J. Amer. med. Assoc. 115:*912-16, 1940.
35. Benjamin, B. and Ratner, M. Hypertension associated with unilateral chronic atrophic pyelonephritis. Occurrence in a child in whom no decrease of blood pressure followed nephrectomy, *Amer. J. Dis. Child. 61:*1051-63, 1941.
36. Oppenheimer, B. S., Klemperer, P. and Moschcowitz, E. Evidence for the Goldblatt Mechanism of hypertension in human pathology. *Trans. Assoc. Amer. Phycns. 54:*69-81, 1939.
37. Saphir, O. and Taylor, B. Pyelonephritis lenta, *Ann. intern. Med. 36:*1017-41, 1952.
38. Jackson, G. G., Dallenbach, F. D. and Kipnis, G. P. Pyelonephritis: correlation of clinical and pathologic observations in the antibiotic era, *Med. Clin. N. Amer. 39:*297-305, 1955.
39. Nesbitt, R. M. and Conger, K. B. Chronic pyelonephritis, *N. Y. St. J. Med. 42:*225-32, 1942.
40. MacKeith, R. Pyelonephritis (pyelitis) in infancy and childhood, *Practitioner 170:*258-65, 1953.
41. DeNavasquez, S. Further studies in experimental pyelonephritis produced by various bacteria with special reference to renal scarring as a factor in pathogenesis, *J. Path. Bact. 71:*27-32, 1956.
42. DeNavasquez, S. Experimental pyelonephritis in the rabbit produced by staphylococcal infection, *J. Path. Bact. 62:*429-36, 1950.
43. Braude, A. I., Shapiro, A. P. and Siemienski, J. Hematogenous pyelonephritis in rats. I. Its pathogenesis when produced by a simple new method, *J. clin. Invest. 34:*1489-97, 1955.
44. Shapiro, A. P., Braude, A. I. and Siemienski, J. Hematogenous pyelonephritis in rats; production of chronic pyelonephritis by *Escherichia coli, Proc. Soc. exp. Biol. Med. 91:*18-24, 1956.
45. Burnet, F. M. *The Clonal Selection Theory of Acquired Immunity.* Nashville, Vanderbilt Univ. Press, 1959, 208 pp.
46. Waksman, B. H. Distribution of experimental auto-allergic lesions. Its relation to the distribution of small veins, *Amer. J. Path. 37:*673-93, 1960.
47. Terplan, K. L. and others. Experimental thyroiditis in rabbits, guinea pigs and dogs, following immunization with thyroid extracts of their own and of heterologous species, *Amer. J. Path. 36:*213-39, 1960.
48. Collins, R. C. Further experimental studies in sympathetic ophthalmia, *Amer. J. Ophthal. 36:*150-62, June (pt. 2) 1953.
49. Merrill, J. P. and others. Successful homotransplantation of the kidney between nonidentical twins, *New Engl. J. Med. 262:*1251-60, 1960.
50. Scholl, A. J. Urologic conditions simulating chronic glomerulonephritis. Chairman's address, *J. Amer. med. Assoc. 111:*1421-27, 1938.
51. Evans, B. M. and Milne, M. D. Potassium-losing nephritis presenting as a case of periodic paralysis, *Brit. med. J. 2:*1067-71, 1954.
52. Smythe, C. McC., Rivers, C. F. and Rosemond, R. M. Comparison of the incidence of bacteriuria among hypertensives and matched controls, *Arch. intern. Med. 105:*899-904, 1960.
53. Robbins, S. L., Mallory, G. K. and Kinney, T. D. Necrotizing renal papillitis; form of acute pyelonephritis, *New Engl. J. Med. 235:*885-93, 1946.
54. Nussbaum, H. E., Bernhard, W. G. and Mattia, V. D., Jr. Chronic pyelonephritis simulating adrenocortical insufficiency, *New Engl. J. Med. 246:*289-93, 1952.

RELATIVE IMPORTANCE OF LATE SEQUELAE OF IRRADIATION IN MAN*

The Seventh Ross Golden Lecture

R. R. NEWELL

Professor Emeritus of Radiology and Biophysics, Stanford University School of Medicine; Scientific Consultant to U.S. Naval Radiological Defense Laboratory, San Francisco, California

IT is indeed an honor to be invited to give a lecture under the name of a teacher so distinguished and so well-loved. I hope many of Ross Golden's pupils are here to see that they have some competition in their admiration of him. I first met Ross Golden during the Radiological Congress in St. Moritz. That was 25 years ago. I still love those noble peaks and that noble head, above the timberline! I have some pictures. (Motion pictures were projected showing many of the radiologists present at the Congress in 1934.)

For more than three score years we have been studying radiation. The accumulated mass of knowledge is impressive in the eyes of the scientist and terrifying to the student. Yet our knowledge is still woefully insufficient and, in fact, downright puny in the eyes of the hygienist. We are asking for statutes to regulate a harmful agent that is practically outside our ken. One cannot smell it, taste it nor hear it, and it is only just possible to show that one can feel it and see it. Except for a few scientists, people have no experience of it and so have developed no intuitions about it. It is almost beyond the benign corrective influence of common sense[1-3]—as is many a time evident in the newspapers. And moreover, many of the effects on human health are subtle at the moment, and will emerge to plague us only after some years or even after many generations.

* Presented at the Meeting of the New York Roentgen Society, held at The New York Academy of Medicine, January 18, 1960.

The opinions expressed are those of the author and should not be taken as reflecting the opinion or policy of Stanford University or of the U.S. Navy.

Somatic and Genetic Injuries

Some radiation injuries appear long after the irradiation, even though no effects were noticeable at the time or in the weeks and months following. We speak of somatic injuries, affecting the person irradiated; and genetic injuries, affecting future generations.

Moral Aspects

The responsibility for somatic injuries is clear. A workman, for example, properly expects not to be exposed to avoidable hazard, and if injured, expects to be indemnified. Genetic injuries are generally less well understood. I would like to present the mutagenic effect as an increase in probability that some unidentifiable person will be defective. If the bad chance eventuates in a visible defect, it is not separable from other inevitable bad chances quite unrelated to the irradiation in question. Moreover, it is likely to be in a generation so far removed that only the most tenuous inference connects it with the person in whom the mutation originated. The chain of responsibility can never be forged between personal cause and personal effect. The radiologist's responsibility is, diffusely, to all posterity, and not for a definite injury but only for a calculated probability.

A parable will illustrate this aspect of genetic injury: A radiological physicist came to make measurements for a young radiologist. They were discussing genetic hazards even while the radiologist gave the injection for an excretory urogram and ostentatiously put a lead shield over the patient's testicles. Later the technician said: "We didn't use the genital shield on the first patient this morning. Do you think he might sue?" The expert replied: "If he does, you could sue, too. If a mutation were actually produced, it might well happen that your descendants and his will have intermarried by the time the inherited defect comes to light." (Figure 1.)

The Unobservability of Genetic Injuries

We have no doubt at all about the reality of genetic injuries. The mutations induced by radiation comprise the same varieties that appear spontaneously, some of them with a frequency up to perhaps 40 per million per generation. The picture of the irradiated woman who gives birth to a monster is not entirely misleading, but such a monster (e.g.,

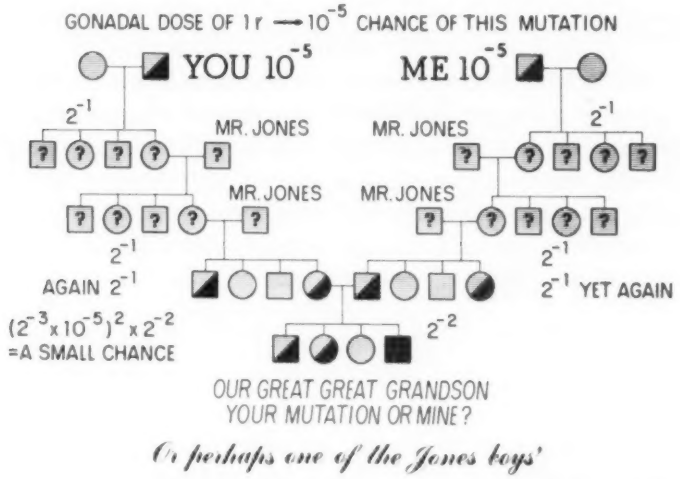


Figure 1. Fanciful family tree illustrating emergence of a recessive mutation.

anencephaly) is a somatic injury, not a genetic one. Embryonic tissues in the stage of differentiation are exceedingly radiosensitive.[4] A serious defect in development may follow an exposure of 25 r at the critical moment in gestation. For most organs, the supersensitive days occur so early that the woman may not know she is pregnant. It has been recommended that abortion be done if it be discovered that a fetus received more than 10 rads between the second and sixth week of gestation.[5] The nervous system spreads its development over most of gestation. Therefore, the fetus cannot be considered really radioresistant at any stage. But such fetal injuries do not pass on to future generations.

The genetic injuries (mutations) may appear in the first generation (perhaps 6 per cent of the 30 generation total) but most of them will crop out as visible defects later, building up to a second maximum around the twentieth generation.[6] And, as I have just said, when they do appear, they will be indistinguishable from the heritable defects that normally (naturally) appear in 2 per cent of babies born. Therefore, we shall not be able to validate our theory of genetic injury from observations on children and grandchildren of a few irradiated women.[7] The best we can hope for is some statistical confirmation, by counting the relative increase in heritable defects in an irradiated population. It appears that Nature has actually done such an experiment for us.

A Possible Exception to the Unobservability of Genetic Injuries

In the State of Kerala (Travancore) in India, some 80,000 people have lived on monazite sand beaches for uncounted generations. The natural radiation there is ten to twenty times what it is in most places. The World Health Organization is supporting a program to examine all these people and to measure, if possible, their differences from neighboring people in the same culture. It is considered rather improbable that the genetic effects will prove measurable.[8]

The Unobservability of Late Somatic Injuries

The sequelae warranting consideration are: 1) leukemia; 2) carcinoma and sarcoma; 3) shortening of the life span. Nephrosclerosis is a serious sequel in some mammals,[9] but only a few dozen instances are reported in man[10]—negligible in comparison with the natural incidence of Bright's disease. These late sequelae are diagnosable and countable, but only statistically referable to irradiation as the cause.

Leukemia

Judging from the incidence among survivors of the Hiroshima bombing,[11] a barely sublethal total-body dose gives a person a one or two per cent chance of developing leukemia in the next ten years. If he should, in fact, become leukemic, then it would be a good bet that the radiation was responsible, since the natural incidence of leukemia is only about 50 per million per year. But a small exposure, say ten times the occupational MPD, is expected to increase a person's natural likelihood of getting leukemia so little that any single instance had better be attributed to natural causes. It has been estimated that one would have to expose six million persons and observe them for ten years to show dependably whether a total body dose of five rads is leukemogenic.[12]

Biological Effect of Minimal Doses

It is not that we doubt that such small doses have a biological effect. In fact, we are logically convinced that they do have. This conviction arises from our conception of the quantization of radiation and the quantization of life. Whichever quantum you look at—the photon, the beta ray, the ion, even the non-ionizing excitation; the man, the organ, the cell, the mitochondrium, the enzyme, the chromosome, the gene—

it's a quantum. Obviously, if the radiation is absorbed at all, one quantum wrestles one quantum and "it will never be the same again".

Set against this hopeless picture is our conception of recovery. Many living molecules are generously replicated. The nuclear factory can supply replacements for most cytoplasmic losses. But our concept of the gene is that it is unique; and moreover, that it is itself the only memorandum that the cell contains to tell how a lost gene is to be reproduced. It's not like that simple quantum state of a K electron. If you knock it out, another is promptly manufactured to order by shucking off a photon from another electron, and this is moved in to fill the defect.

Let us admit that all these fine things are only figments of our imagination. We find them powerful tools for predicting and managing the physical world we live in. (Not the political world, more's the pity!) As Einstein[13] says, they are free inventions of the human mind. But we must continually check them against observations to see if they need amendment.

The Physiological and the Empirical Approach

The empirical approach notes the anecdotal appearance of cancer and of leukemia in persons who have been exposed to radiation. Experiments on animals confirm the carcinogenicity and leukemogenicity of radiation. And they show us some other things besides—notably that animals recovered from sublethal doses of radiation do not live as long, on the average, as those not irradiated.

Many scientists have developed empirical formulae for these effects, i.e., mathematical models to fit the observed data. Mewissen[14, 15] has discussed some of these for lethal endpoint, assuming an exponential recovery, but with a small irrecuperable residue of injury. Krebs[16] estimates ten per cent irrecuperable. Alpen[17, 18] observes that the recovery rate is not constant, but is a function of the dose. For hematopoietic function of bone marrow, he was able to show marked heterogeneity within a supposedly homogeneous rat population, contradicting simple notions of chance hit effects. His subpopulations showed an exponential slowing of recovery rate as dose accumulated.

Perhaps we ought to have an equation for every vital function. Certain it is that the induction of leukemia for some dosage schedules appears to show a negative recovery rate, a single dose being less effective than the same total given in several fractions a few days apart.[17, 19, 20]

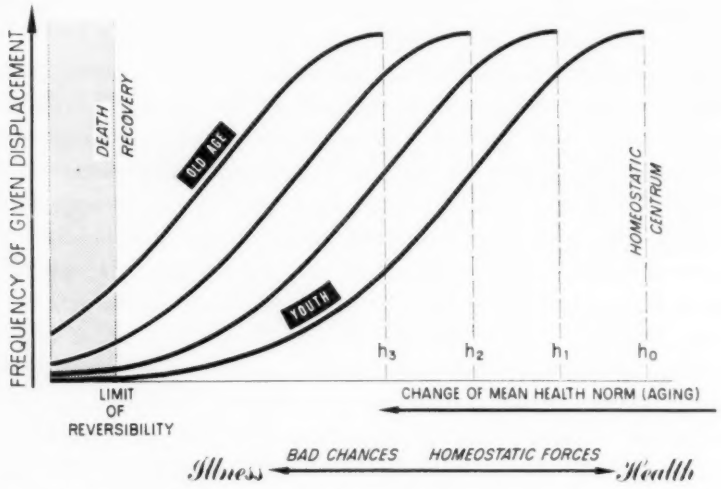


Figure 2. Picture of Sacher's speculative model to explain the exponential increase of death rate with arithmetic increments of injury. Age and injuries displace the homeostatic mean of health, $h_0 \rightarrow h_1 - - - h_3$, so that deviations reach the irreversible lethal level with greater frequency.

As Brauer[21] said, considering radiation effect as equivalent to premature aging, the several organs grow old at different rates, and an irradiated animal can be looked upon as an age chimera.

For the lethal effect of multiple doses I find Sacher's[22] theory quite persuasive. His notion is that life depends on a large number of homeostatic mechanisms, all subject to perturbations and inefficiencies. When the sum of all the perturbations exceeds a certain amount, the change becomes irreversible, homeostasis fails and life ceases. He says that diseases and injuries and radiation displace the average perfection of the homeostatic mechanisms, so that the critical extreme perturbation comes to have a greater likelihood. He shows mathematically how, in this model, a linear displacement of the mean equilibrium results in an exponential increase in the chance of death (Figure 2), thus fitting the Gompertzian[23] function (see p. 391-2). Jones[24] has speculated that any severe disease (as well as irradiation) makes this exponential rise in the death rate (the so-called force of mortality) begin earlier. However, there is some doubt about the generality of this rule.[25]

These are all classed as empirical formulae. They are hard to validate even in experimental animals when the doses are small and the ob-

servable effect infrequent (as in tumorigenesis and leukemogenesis) or small (as in shortening of life). They get little logical support from biological argument, for they are not founded on a quantitative understanding of the interplay of physiological processes.

The Analytical Approach

Sacher[26] has remarked on the need for such basic knowledge. Most of our animal experiments have been done on small rodents. When doses are small and effects are variable and infrequent, the numbers needed are inconveniently large for experiments on animals comparable in size to man. There have been a few irradiations of burros[27] and swine.[28] The swine tolerated 50 r per day better than the burros tolerated 25 r per day. These two species are rather different, but examples are not lacking to illustrate the diversity of animals thought to be quite similar; for example, rabbits and guinea pigs, which prove to be near the extremes of the range of radiation sensitivity among non-hibernating mammals. These things make me doubt the "scaling factors" based on size or on presumed "biological relationship". I do not see that measurements on "our near-cousins", the primates, are *a priori* more pertinent than those on mice.

We all agree that the "extrapolation" from mice to men should be based on a quantitative understanding of all the physiological systems, their equilibria and controls, and the effect of radiation on each, together with an adequate quantitative theory of homeostasis. A comparison of physiology under injury and recovery from small doses in several mammals could then provide a believable logical route for predicting the effects in man. We would be more willing, then, to make judgments and take action on those radiation injuries that are individually unobservable. Some day we shall perhaps have the needed information. Everyone agrees we do not have it now. And radiation is upon us. We can't wait!

Animal Experiments

Leukemia has been studied a great deal in animals. It is very readily induced by radiation in some strains of mice. Most mouse leukemia is lymphatic, but there is at least one strain that develops granulocytic leukemia.[29] It was in the mouse that Kaplan[30] showed lymphoma induction in unirradiated thymus transplanted into an irradiated recipient.

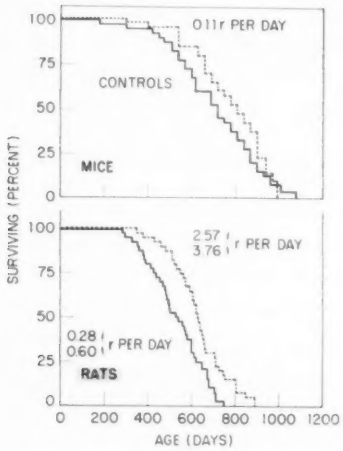


Figure 3. Death curves showing better longevity under low level gamma irradiation. The mice were reported by Lorenz[33], the rats by Carlson.[34] The latter curves were made smoother by combining the two lower dose groups and the two higher dose groups and treating the 44 rats in each combined group as a single sample.

Viral (transmissible) leukemia seems beside the question as long as we are unconvinced of the transmissibility of human leukemia.[31]

Malignant Tumors

Carcinoma and sarcoma are readily induced in many animals by heavy irradiation. Many attempts have been made to develop a good theory of how cancer arises—of which those based on somatic mutations have the greatest present vogue. None is sufficiently attractive to make me wish to argue it here.

Longevity

Many serious attempts have been made to determine the rate of recovery from large and moderate roentgen doses. I have already referred to some.[14-17, 20, 22-24] There are still many points of disagreement. It is generally thought that the younger animal tolerates large doses better than the older one. There is some evidence, however, that the chain of reactions that shortens life after non-lethal doses has a latent period.[32] In the aged animal there is less time remaining in which the increased force of mortality can operate.

A number of investigators have subjected large groups of animals

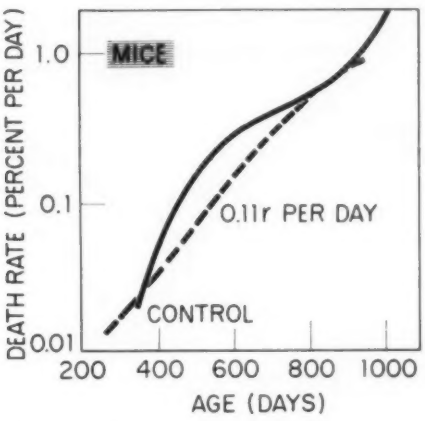


Figure 4. Gompertzian transform for the mouse data of Figure 3. The death rates were taken from Lorenz's published smooth curves. The difference in death rates is significant only among those that died younger than 700 days (compare Figure 3).

to single, multiple or continuous exposures to find out the effect on longevity.[19, 20] It is from these that Hardin Jones[24] has estimated the proportionate loss of life expectancy caused by radiation. His estimate for man is ten days of life shortening per roentgen of whole-body exposure. There seems to be no doubt about the life-shortening from large single doses. The continuous or repeated small doses, however, run into trouble with the lack of invariance of recovery rate and its marked species differences. The swine and burros already referred to[27, 28] had similar sensitivity to a single large dose, but daily irradiations showed that the swine had twice as good a recovery rate.

In a number of experiments on small mammals, small, daily or continuous irradiations have appeared to lengthen the life span. Two examples are Lorenz's mice[33] and Carlson's rats.[34] The survival curves (Figure 3) show what appears to be a beneficial effect of a small amount of gamma ray. Physicians must be skeptical. Therapy based on such a notion did once have considerable vogue, but would now be called quackery.

The age-specific death rates calculated from these data are plotted on semilog scale (Gompertzian) in Figures 4 and 5. It is evident that the force of mortality is abnormally high early in the life of Lorenz's control mice, but that the death rate among the irradiated ones finally

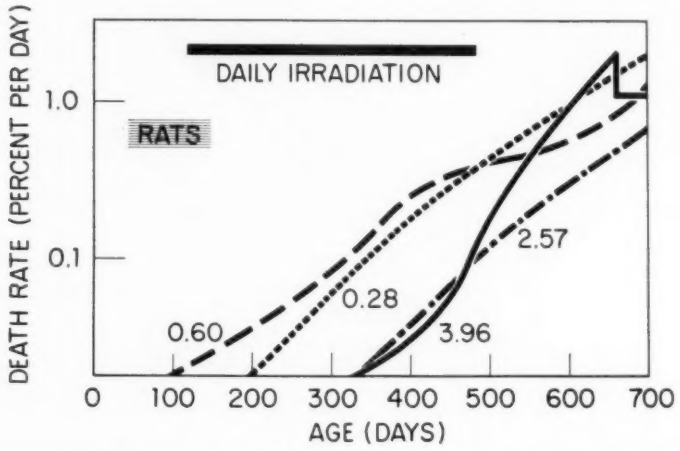


Figure 5. Gompertzian transform for the four 22-rat groups that are combined into two groups in Figure 3. The published data were smoothed by eye, with estimated uncertainty 1 or 2 decibels in the Gompertzian.

catches up. Among Carlson's rats, also, the lightly irradiated ones start out with a high death rate. Only the most heavily irradiated ones finally overtake the others, demonstrating an unequivocal life-shortening effect after most of the 1.4 kr total accumulated dose had been inflicted. On the face of it, one would say that small amounts of radiation had acted therapeutically on whatever disease was causing the middle-aged mortality. One hesitates to accept such a conclusion, however, without knowledge of the disease responsible and without additional similar experiments. In some strains of mice it appears that a proper dose of radiation can reduce the leukemia incidence by therapeutic effect on the natural disease more than it increases the incidence by irradiation leukemogenesis.*

Partial Body Irradiations

It is well known that shielding the spleen, or even one extremity, makes as much as a 2:1 difference in the exposure required to kill an animal. But there are not a great many experiments reported that were designed to show the quantitative relationship of fraction irradiated to

* Note added later: G. J. Neary in *Nature 187*:10-18, 1960, discusses the effect of radiation on aging in mice, citing some of the reports noted above, together with some as yet unreported. He prefers a model featuring a long induction time, after which the acceleration of the age-specific death rate goes its own way.

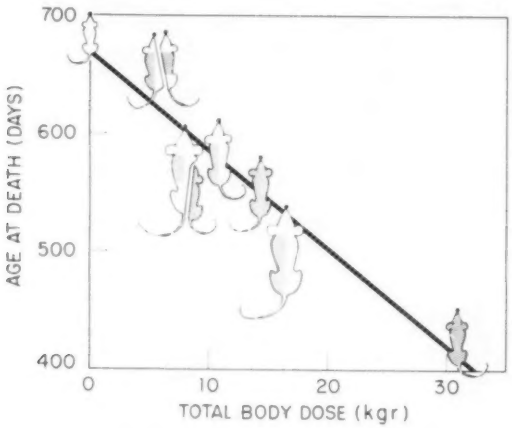


Figure 6. Plot of Kallman and Kohn's data with calculated regression line of longevity on integral (total body) dose. The shaded areas show the portion of mouse irradiated. The sizes of the outlines show the reported standard errors.

effect on longevity. Figure 6 is plotted from data reported by Kallman and Kohn[35] (by-product of other research, they say). Obviously the larger the dose, to a part of the body or to the whole body, the shorter the life. The linear regression line shown does not fit very well. The fit could be improved by choosing favorable constants, e.g., second power of tissue dose and a factor of 2 when the entire body is exposed. Dr. Kohn thinks the factor depends on which parts (organs) are irradiated, and so do I, but data to prove it are not at hand.

Clinical Evidence

Figure 7, reproduced from Kohn's report,[36] shows the survival of two groups of women, both operated on for cancer of the breast, with only one group given postoperative x-ray. No difference in mortality has become evident so far (15 years).

Figure 8 is from my report[37] on longevity of women cured of cancer of the uterine cervix by irradiation. They appear to have lost an average of eight months of life, attributable to the cancer and its treatment. But those who survived five years then matched the standard life table in mortality. The patients in Stage I did not show this early mortality, but stayed always above the average life expectancy of white

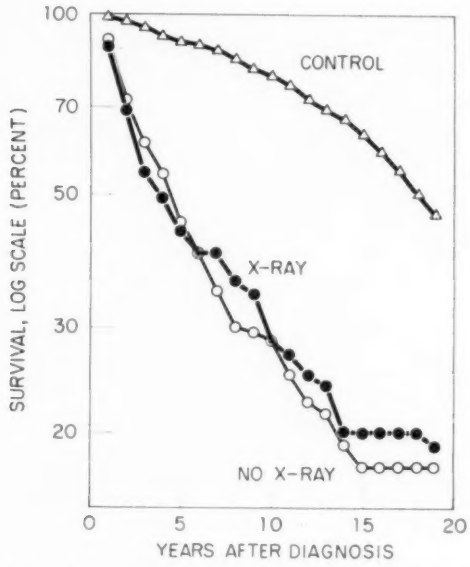


Figure 7. Kohn's data on survival of women operated on for Stage II cancer of the breast, and given routine post-operative x-ray treatment, or not irradiated.

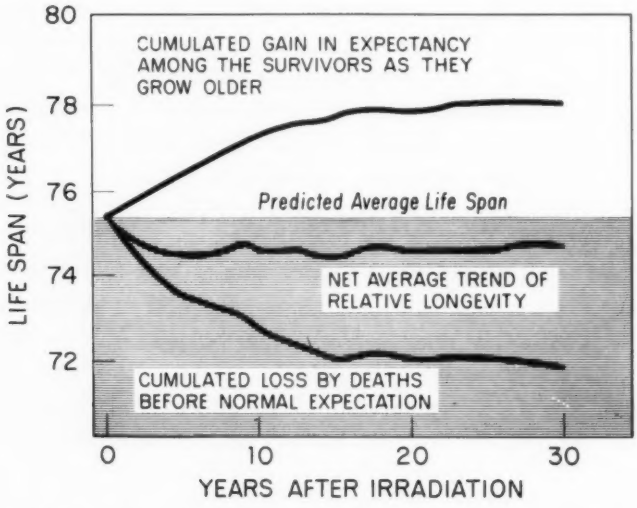


Figure 8. Survival among 217 women who remained free of recurrence after irradiation cure of cancer of *cervix uteri* (5 megagram rads of radium or 30 to 40 megagram rads of x-ray and radium combined). The predicted average lifespan is the average age plus the average life expectancy (U.S. 1940 census) at time of treatment.

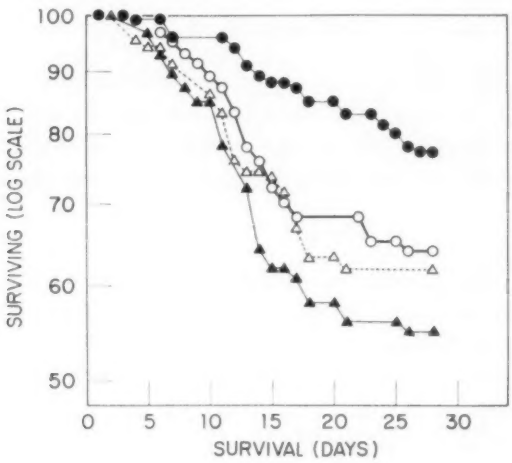


Figure 9. The variability in survival curves observed in four groups of 64 mice all given the same dose of x-ray at the same time.

females in the 1940 census. The absence of perceptible life-shortening from these large doses should quiet our apprehensions about diagnostic radiography, in which the doses are much less than one tenth per cent as large.

Confidence Limits

Even the most inbred races of laboratory animals, or their genetically uniform first generation hybrids, show a lamentable variability in length of life. Some of this arises from laboratory conditions—microclimate, fighting within cages or even threats from adjacent cages, enzoötic and adventitious diseases, etc. If disease-free colonies are less variable, we still don't know whether we can safely argue from them to disease-ridden urban populations. Figure 9 illustrates the possible pitfalls in the path. Cronkite at NMRI exposed 256 presumably normal mice all to the same dose. They were arranged in a circle at uniform radial distance from the target of a megavolt x-ray machine. Beginning with #1, every fourth mouse was chosen to make group A, the same beginning with #2, #3, and #4 to make groups B, C, and D respectively. I have argued[38] that such chance differences have the capability of misleading an investigator who is insufficiently wary.

Human Data

Many of the data on man are pretty unsatisfactory.[39] I could cite the debate on "what is really the LD 50 for man" at the Congressional Hearings last June.[40] Data on age at death of radiologists and other medical specialists are now thought not to prove any life shortening.[41]

Human Leukemia

It is well established that radiologists are more likely to die of leukemia than are other physicians—perhaps five times more likely.[42] The incidence of leukemia among the survivors of the Hiroshima bombing has been very high,[11] and has been well correlated with the exposure to primary radiation as deduced from the person's location, with allowance for shielding by buildings. The 13,000 patients followed in England[43] after x-ray treatments for spondylitis, however, compose the only large group in which the dose of radiation was measured. It is noteworthy that most of the cases were acute leukemia; only nine out of the entire 37 were of the common chronic granulocytic type. It is also noteworthy that the leukemogenesis does not continue indefinitely, but already appears much diminished, eight years after irradiation among the Hiroshima cases and six years after last treatment in spondylitis series.

Extrapolation to Small Doses

Court-Brown and Doll[43] argued for a linear relationship between tissue dose in the spinal bone marrow and the subsequent likelihood of developing leukemia. Lamerton[44] notes that their presentation of the dose as the mean dose in (entire) spinal bone marrow introduces a presumption of linearity. The same presumption is reinforced in the recalculation (in their Appendix D), attempting to make allowance for the observed tendency of the leukemia cases to appear in the third and fourth years after irradiation. Loutit[45] thinks that the linear extrapolation is based "on a theory of carcinogenesis that has been discussed for many years and found wanting, certainly as a sole cause." Mewissen[14] decries the assumption of a random hit effect with approximation to a linear relationship over a limited region of small doses. He argues for a normal or log normal random distribution of individual susceptibilities for which probit analysis would be efficient. Brues[46] notes

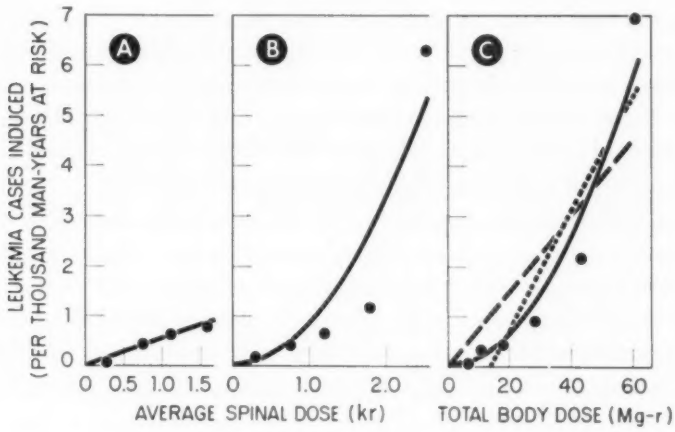


Figure 10. Eleven thousand men treated in England for spondylitis, among whom appeared 37 cases of leukemia. *A*. Patients irradiated over spinal and sacroiliac regions only. Linear regression gives a very good fit. *B*. All the patients. Regression on the square of the dose averaged over spinal marrow gives better fit than linear regression, but still with error > 15 times as large as in group *A*. *C*. Regressions on total body integral dose. . . . . Calculated regression indicates a threshold. - - - - - Least squares fit assuming no threshold, which makes the standard error of prediction 40% larger. ————Regression on the square of the dose, which fits twice as well as the linear regression, and deteriorates but little if made go through the origin (no threshold). • Points from the published tables, crude leukemia morbidity less the assumed natural incidents.

that the spondylitis cases fit a square-of-dose relationship better than a linear one.

Since we have become concerned about the number of leukemia cases that will be engendered by prospective industrial exposures and by the absorption of radioactive fallout, it seems wise to make the best use we can of these data.[43]

Prediction for Small Doses

I am pretty well convinced that the curvilinear (quadratic) regression is the best presumption. Figure 10 shows correlations of leukemogenesis with x-ray dose, using Court-Brown's data. Only for narrowly limited irradiations does the linear model give a fit. Since we do not know leukemia induction from small doses by observation, but only through our logical deduction from what comes after large doses, I

think we should stick to the logical deduction. This would seem to mean using the best model we can forge, and abiding by it. Until we have better evidence, we ought to put our trust in the large series analyzed according to total body integral dose, for this alone is comparable to the kind of exposures we are thinking about in industry, and from fallout. The selected set of 18 leukemia cases narrowly irradiated over the spine is certainly not a good starting point for the extrapolation.

With the use of a log transform, the spondylitis data give a fair correlation ($r = 0.92$) with a slope about 1.6 Yet a linear regression on $(\text{dose})^2$ gives a higher correlation, presumably because of matching on arithmetic mean rather than geometric mean. Even the best model has poor efficiency. In extrapolating to small doses, one's confidence is soon shaken by observing a standard error a hundred times as large as the effect predicted.

The fit is not good enough to make the choice of regression coefficient very critical, but the following is about as good as one can get, assuming no threshold:

$$\text{leukemia produced per million man years} = 1.59\ (\text{Mgrad})^2$$

Taking this at face value, a total body dose of half a megagram-rad which might be absorbed from a 15 r maximum permissible exposure would produce about one chance in two million (per year) of inducing leukemia. This is about one per cent of the natural leukemia incidence. If you think that chances of this order are without practical meaning, you should multiply it by the world population and get 1250 total leukemia cases. Of course, only a very few persons get an MPD; the average exposure among thousands of exposed workmen runs near 0.2 r per year. Calculating on $(\text{dose})^2$, one now predicts a yearly average leukemia induction of one in ten billion. The natural leukemia morbidity is about 50 per million, with unexplained differences of 30 per cent between rural and urban populations.[47] Among large United States cities the standard deviation is 14 per million.[48] In the face of such variations, a change of a fraction of a per cent predicted by extrapolation over a couple of orders of magnitude must be almost meaningless to a scientist. To a humanist, however, such extrapolations have real oratorical usefulness, because he translates them from percentages to men.

Strontium-90

The leukemia induction from Sr^{90} in the bones (from the world-wide fallout after large nuclear bomb testing) is being argued vigorously.[49-51] The measurements reported from fallout stations show many millicuries per square mile in the Northern Hemisphere, and more is still coming down. Measurements of the bones, especially in young children, show several $\mu\mu$C of Sr^{90} per gram of calcium. But the deposit is not uniform; the growing portions of the bones get much the largest amount.[52, 53] For a given body burden, of course, the greater the concentration in some portions of the bone, the smaller the volume of tissue at risk. If the hazard is a linear function of the dose, or of the dose-rate, the hazard is unchanged by the distribution. But if leukemogenesis is an increasing function of dose or dose-rate, then uneven distribution increases the hazard from a given body burden.

In CFN°1 female mice, Finkel[54, 55] found leukemia appearing sooner, the larger the dose of Sr^{90}, although even a small dose would eventually produce a large number of leukemia deaths.

Bone Tumors

Only a few dozen cases have been reported of bone tumors in man from measured external irradiation.[56, 57] The best human evidence is that supplied by patients with radium in their bones, who developed bone cancers after 5 to 30 years. In trying to deduce the Sr^{90} hazard from these data, one has the difficulty that the radium induction was by alpha rays, which have a very high RBE, compared to Sr^{90}'s beta rays. Finkel compares the carcinogenicity of Sr^{90} and Ra^{226} in the bones as shown in experiments with several sizes of mammals. She concludes that the accepted maximum permissible body burden of Sr^{90} (then 1 μC, now 2 μC) is not unreasonable. However, she made no allowance for the extreme spottiness of Ra deposits in bones, and the very different distribution when given in one dose and when given slowly over a long time.

Radium in the Bones

Rowland and Marshall[58] found that the hot spots (Figure 11) hold about half the body burden. Among patients developing sarcoma many years after ingestion or injection of radium, the calculated dose in

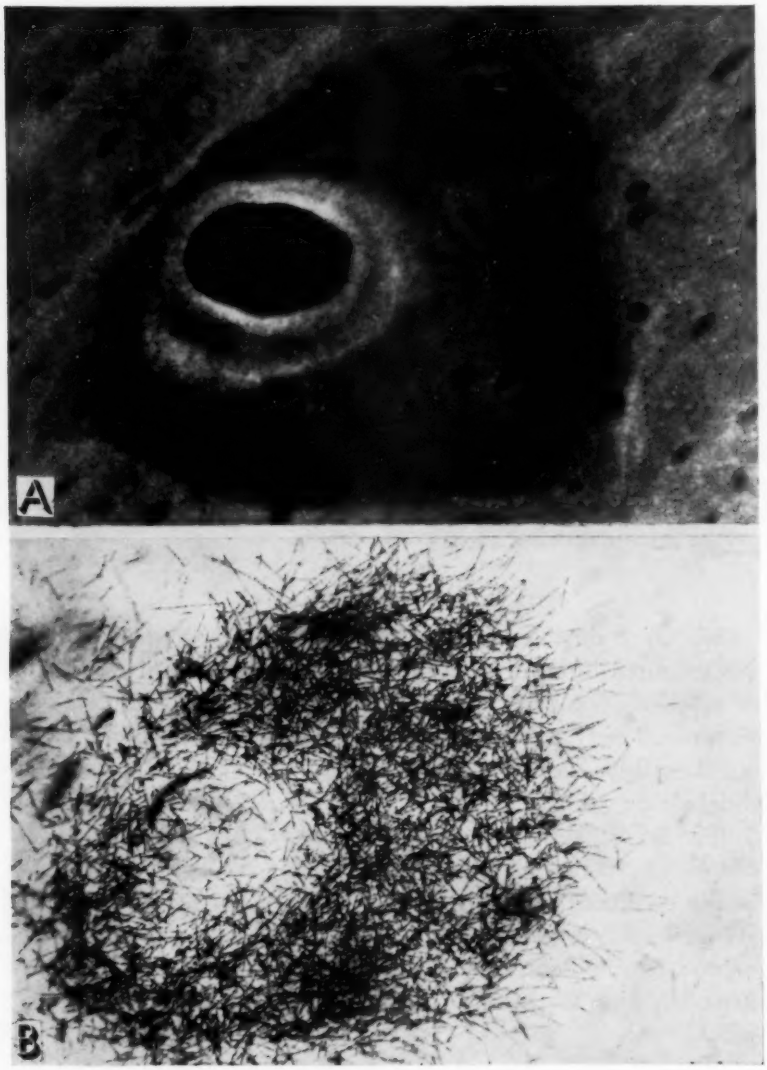


Figure 11. *A*. Photomicrograph of bone from a case of chronic radium poisoning.

B. Radioautograph of same section showing concentration of alpha rays close around the Haversian Canal. (Courtesy of R. E. Rowland and *Radiation Research*.)

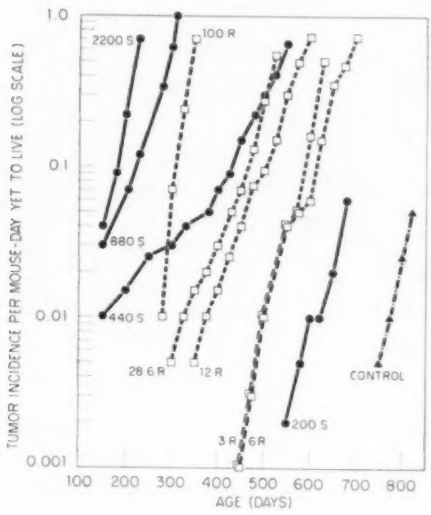


Figure 12. Bone tumors in mice after single doses of Ra^{226} or Sr^{90} (replotted on log scale from Finkel's published plot).

hot spots varied from 10,000 rads to half a million; in the rest of the bone it varied from several hundred rads to several thousand. Three situations appear possible among patients with ultimate body burdens from 1 μC to 10 μC of radium: 1) tumorigenic dose in bone generally, with supralethal dose in hot spots; 2) tumorigenic dose in hot spots only, 95 per cent to 99 per cent of bone being below tumorigenic concentration; 3) tumorigenic concentration limited to a shell (about 0.1 per cent of total bone) between necrosis in the hot spots and inefficient tumorigenesis in the rest of the bone. Consequently, there must be a range of radium dosage for which one should expect a very uneven relationship of tumorigenesis to body burden. This would be in contrast to the expectation for similar effective doses of Sr^{90}, because the spottiness of strontium is much less extreme.

Finkel's[59] mice did indeed show a greater effect from 3 μC of radium than from 6 μC. Moreover, the antedating of the tumor incidence changed much more slowly with dose for Ra^{226} than for Sr^{90} (Figures 12 and 13). This throws some doubt on her inference of Sr^{90} hazard for man based on Ra^{226}/Sr^{90} ratio for tumor induction in animals and the apparent 0.8 μC Ra^{226} threshold for tumor induction in man.

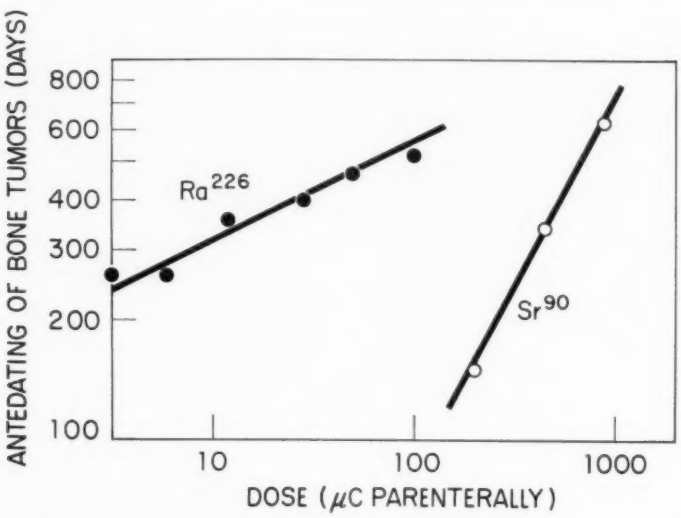


Figure 13. The data of Fig. 12 plotted to show the relation of tumorigenesis (as antedating tumor appearance) to the dose of Ra^{226} or of Sr^{90}.

Yet I don't know any better way to get at it. We can't wait the twenty years necessary to find out by direct observation how carcinogenic the Sr^{90} from the fallout will prove to be.

The Responsibility of Radiologists

Radiologists were the first to suffer from the bad effects of radiation and the first to lend their support to the campaign for controlling radiation hazard. May I therefore write "we" when referring to the radiological profession and the National Committee for Radiation Protection? We agree that the radiologist has the same duty as the industrialist to protect his employees and people generally from the bad effects of the rays he is using. Our handbooks[60] have tightened up the recommended controls and made successive reductions in the MPD. Even though we know now that somatic injuries can result from doses previously thought innocuous, yet there is no evidence that any person has been injured by exposures near the level of the old MPD even before it was reduced. I feel sure that the *genetic hazard* was the principal reason for reducing the MPD, and that it still dominates our thinking in regard to small exposures.

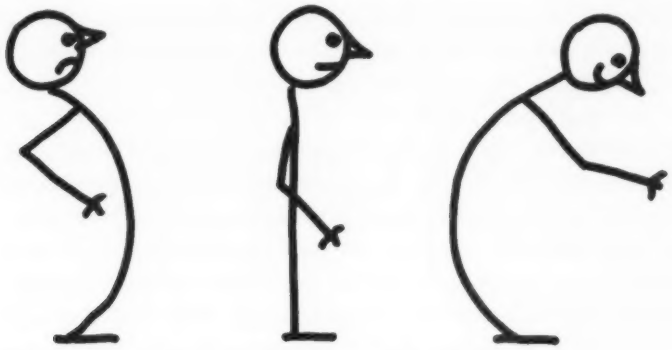


Figure 14. Range of attitudes in radiation control:
A. Leaning over backward (to avoid possible criticism).
B. Bolt upright.
C. Reasonably flexible.

The Nature of the MPD

The MPD purports to be a limit on the exposure of the individual. This can easily be taken to imply that a larger dose might hurt him. The National Academy of Sciences was actuated by this implication when it recommended that every person keep account of his exposures and that nobody be permitted to accumulate a total above 50 r.

I think that it is abundantly evident that the MPD is not, in fact, a dose that borders on injury to the person exposed. I think that the MPD is a disciplinary rule to keep the average exposure low. If you run your shop so that no person is at all likely to get more than 5 r in any year, then the average exposure among scores or hundreds of employees will be much lower, perhaps 0.5 r or 0.2 r for the year.

This does not mean that the MPD should be relaxed. It does not mean that overstepping the MPD is to be condoned. It is a breach of discipline and should be handled accordingly. No doubt there will still occur the rare improbable accident in which some exposures may be very large indeed.

The Shielding Rules

In order to live within the MPD, radiologists are given rules for shielding (Handbook 60*). In previous handbooks the worst circum-

* Soon to be superseded by HB76.

stances were always presumed. This "leaning over backward" is a lovely selfconscious attitude, but it does not really become a scientist. The fact is, we do like to have scientists hypercritical about their observational data and logical conclusions. Moreover, we do like to have them eager in exploring new ideas and activities. But having come to the best conclusion that he can, the scientist should have the courage to stand up for it. I would like to see him bolt upright (Figure 14).

In developing the rules for HB 60 some allowance was made for the known facts that x-ray tubes are operated only intermittently, that the useful beam is not always pointed at the wall, and that scattered radiation is small in amount and sometimes softened in quality, but has a "four pi" distribution. Also that some spaces (e.g., corridors) are not continuously occupied. But no allowance has yet been made "officially" for the obvious fact that in clinical radiology the major portion of the useful beam is absorbed or scattered by the patient. If we do what we should do in the way of coning down to the size of the film, this occultation by the patient will make the amount of radiation that reaches the walls of the room very much less than what is now being assumed for calculating the required attenuating barrier.**

For many years radiologists considered skin erythema the threshold of injury. Statistical correlation of suberythema irradiation of the thymus in infancy with development of thyroid cancer in childhood is just one of the things that has increased our appreciation of radiation's capacity for harm.[61, 62] Recently, Alice Stewart[63] has collected information on mothers of children dying of leukemia or cancer and has estimated that 7 per cent to 9 per cent of malignant disease has its origin in maternal pelvic radiography.† Clinical radiography has come to be used very widely and frequently in the United States and in Europe. Attention has been focussed on the average gonadal dose to the population, estimated variously from a small to a large fraction of the natural irradiation.[64-67] Somatic effects have not been thought likely from the small doses used in diagnostic radiology. But even these small doses should now be considered perceptibly hazardous when the fetus in utero is exposed.[4, 5] However much or little the genetic and somatic

** Smith, S. W. and Brooks, J. R. Atompraxis 6:77-82, 1960, report measurement at the walls of radiographic rooms in routine clinical use.

† Since giving this lecture I have heard indirectly that more thorough statistical analysis of these data rather lessens the degree of confidence warranted in the conclusions quoted.

effects from radiographic exposures may turn out to be, there is not much doubt about what we radiologists ought to do:

To Minimize Exposure in Radiography

1. Always use a cone or diaphragm to limit the useful beam to the area of interest, certainly within the size of the film. If corners or margins of the film are unexposed, the radiologist can reassure himself that his technician is living up to this ideal. I have called this "the three cornered film" (tcf) or the "Silver Lining."

2. Use high kilovoltage, except where the particular examination is more effectively done otherwise. I think of two examples: a) Calcifications, as in gallstones, should be sought with the lowest kilovoltage compatible with immobilization and the thickness of the part. b) Iodine shadows are most visible when the tube is operated at 70 kvp.[68]

3. Testicles should be shielded from the useful beam, and so should ovaries unless that area is in diagnostic question.

4. Fluoroscopy should be done routinely at high kilovoltage, using a Bucky grid. The fluoroscopic beam should be measured and for routine work show < 6 r/min, with hvl > 2.5 mm Al. And most important! The fluoroscopist's eyes should be dark-adapted.

5. Fluoroscopic image amplification is extremely effective for reducing the exposure. Extravagant use of cinema exposures could dissipate all the profit, of course.

All these precautions will keep our patients, their physicians and ourselves convinced that we're being conscientious. I do not think that diagnostic radiology is much of a threat to public health, but I do think that we radiologists should aim to be a shining example to all who use radiation.

Calculated Hazards

We have had several years of public controversy about radiation injury. The AEC is regularly accused of "playing down" the hazard from fallout, especially the carcinogenesis from Sr^{90} and the genetic effects of Cs^{137}. Both are still coming down from the stratosphere and each has a half-life longer than a human generation. The levels of human exposure are so low that no effect can be observed, nor can we ever hope to observe any. By choosing likely mathematical models, we calculate the leukemia morbidity that will result (Figure 10),

and the carcinogenicity, too. And we calculate the extra mutations that will be added to the fine assortment that the human race already harbors. We take account of the long half-life of C^{14} and of the mutagenic efficiency when the disintegrating carbon atom is in a gene. One can find published predictions of 25,000 extra cases of leukemia in the next two generations and of 10^5 extra defective children in the next 30 generations from even the small present concentrations from bomb testing.[69-71] Let us not quarrel with the figures. Present calculations will have to stand until we get more precise information on which to invent better formulae and to measure more precise parameters.

Value Judgment

What must impress everyone is the wide difference in emotional response to the same figures. The hereditary defects resulting from the predicted 0.1 per cent increase above the natural mutation rate will be "lost" within the normal 2 per cent incidence. The induced leukemia cases, too, amount to but a few thousandths of the natural incidence. Such small percentage effects are calculable but not observable, and the persons affected will not be identifiable. Nevertheless, for some minds and hearts, these calculated persons become real persons. For such minds, the calculated leukemogenesis is not "a negligible percentage of natural incidence," nor "unimportant compared to automobile fatalities." For them, it means so many living persons doomed to die on account of our bomb testing. They believe that this is intolerable—that the wanton destruction of even one human life is not to be condoned.

Human Lives, Identified and Unidentified

There is, I am sure, a moral difference between an identified human life and unidentified human lives. The identified human life is priceless, and I will expend any amount of effort to save it. This is our ideal, and I think it is visible in the actions of large numbers of persons in our culture.

But unidentified human lives (like starving people in over-populated countries) are only a statistic, or at best a biological phenomenon. If we should react to them as we do to the identified life in danger, we should destroy ourselves in excess activity, or else take refuge in a psychosis. I think the difficulty is one that has often arisen to plague

those who make use of mathematical models—namely, trouble with infinities.

The Infinite Value of a Human Life

When we say, "a human life is infinitely precious," we are in the realm of everyday semantics. We know what we mean and others know what we mean. But when we say, "every human life is infinitely precious," we are stating a logical proposition (all A is B) accepted as a hypothesis for further logical argument. We take it at its face value. Mathematicians will write

$$V_L = \infty$$

It then becomes impossible to equate the value of a human life to anything that has a finite value. Lives can only be balanced by lives, and logically they lose contact with the general furniture of the world, which we arrange in some sort of value-order.

No wonder they disagree while citing the same result—those who expect 1/3 of 1 per cent increase in hazard and those who anticipate 25,000 man-made cases of leukemia in the next two generations.

There is another infinity here, I think, that needs a long cool look; namely, the infinite value to a man of his own self-respect. This used to be called virtue, but that is a poet's word now. It is to be contrasted with morality. Morality concerns what society thinks of a man's actions; virtue concerns what a man thinks of his own actions. No doubt virtue has its original roots in morality; but in some souls, usually accounted admirable, virtue has attained an independent growth. Defense of our own self-respect often leads us into illogical paths, but only if we are tolerant of illogic or can keep it hidden.

Summary

The genetic and somatic injuries to man from small exposures to radiation are commonly predicted "by extrapolation" from the observed effects of larger exposures of man and other mammals. The predictions are impossible to validate. When the injuries become observable, they cannot be distinguished from spontaneous troubles of the same sort. We develop the best models that we can for the predictions. Having done so, we should guide our actions by them, accepting their logical implications, including calculated fiducial limits, until a better model is found. The several important radiation injuries that

emerge long after the exposure are discussed, along with the man-made causes of such exposures.

The evaluation of a human life is seen to be sentimental and non-logical. We try to be logical about the bad chances that emerge as injuries that are relatively infrequent but absolutely large in number. We appear to be confused. The logical confusion is shown to arise from the infinity assigned as the proper value of a human life.

REFERENCES

1. Stone, R. S. Common sense in radiation protection applied to clinical practice, *Amer. J. Roentgenol. 78*:993-99, 1957.
2. Newell, R. R. Common sense evaluation of radiation exposure in clinical radiology, *Amer. J. Roentgenol. 80*:917-25, 1958.
3. Miller, J. E. and Swindell, G. E., Common sense in the diagnostic use of x-ray, *J. Amer. med. Assoc. 170*:761-65, 1959.
4. Russell, L. B. Effects of radiation on mammalian prenatal development, *Radiation Biology*, A. Hollaender, edit. New York, McGraw-Hill, Vol. 1, pp. 861-918, 1954.
5. Hammar-Jacobsen, E. Risk of parenthood and risk of subsequent parenthood, cited in *Rep. of U.N. Scientific Comm. on Effects of Atomic Radiation, Suppl. 17 (A/3838)*, New York, 1958, p. 97. (From U.N. Document A/AC.82/G/R.220, Denmark, 1955-56.)
6. Neel, J. V. In *Biological and environmental effects of nuclear war*, Hearings before the Special Subcommittee on Radiation, U.S. Congr., Jt. Comm. on Atomic Energy, Wash., June 1959, p. 627.
7. Kaplan, Ira I. Genetic effects in children and grandchildren of women treated with small doses of x-ray, *Radiology 72*:518-21, 1959; Newell, R. R., Letter, *Radiology 73*:275, 1959.
8. WHO Technical Report No. 166, Effects of radiation on human heredity, Geneva, 1959.
9. Furth, J., Upton, A. C. and Kimball, A. W. Late pathological effects of atomic detonation and their pathogenesis, *Radiat. Res.* (Suppl. I): 243-64, 1959.
10. Reed, B. L., Jr. Radiation nephritis, review, *Amer. J. Roentgenol. 83*:88-106, 1960.
11. Wald, N. Leukemia in Hiroshima City atomic bomb survivors, *Science 127*: 699-700, 1958.
12. Buck, C. Population size required for investigating threshold dose in radiation-induced leukemia, *Science 129*:1357-58, 1959.
13. Einstein, A. in *Albert Einstein, Philosopher-Scientist*, P. A. Schilpp edit. New York, Tudor Publ. Co., 1951, p. 13.
14. Mewissen, D. J., Comar, C. L., Trum, B. F. and Rust, J. H., Formula for chronic radiation dosage versus shortening of life span, *Radiat. Res. 6*:450-59, 1957.
15. Armitage, P., Court-Brown, W. M., Doll, R. and Mewissen, D. J., Dose-response relationship in radiation leukemia, *Nature 184 (Suppl. 21)*: 1669-70, 1959.
16. Krebs, J. S., Brauer, R. W. and Kalback, H., Estimation of the non-recuperable injury caused by ionizing radiation, *Radiat. Res. 10*:80-88, 1959.
17. Alpen, E. L. In: *Radiological Hazard Evaluation*. (See ref. 6, p. 516.)
18. Baum, S. J. and Alpen, E. L. Residual injury induced in the erythropoietic system of the rat by periodic exposures to x-radiation, *Radiat. Res. 11*:844-60, 1959.
19. Kaplan, H. S. and Brown, M. Quantitative dose-response study of lymphoid tumor development in irradiated C 57 black mice, *J. nat. Cancer Inst. 13*:185-

208, 1952.

20. Mole, R. H. Patterns of response to whole body irradiation. In: Effects of dose rate and protraction: symposium, *Brit. J. Radiol. 32*:497-501, 1959.
21. Brauer, R. Discussion of Kohn's essay, *Radiat. Res. (Suppl. 1)*: 240, 1959.
22. Sacher, G. A. On the statistical nature of mortality, with especial reference to chronic radiation mortality, *Radiology 67*:250-58, 1956.
23. Gompertz, B. On the nature of the function expression of the law of human mortality, and on a new mode of determining the value of life contingencies, *Phil. Trans. Part II*, 1825, pp. 513-85.
24. Jones, H. *Lifespan effects.* (See ref. 6, p. 592.)
25. Curtis, H. J. and Gebhard, K. L. Radiation-induced ageing in mice, *Progr. nucl. Energy (Biol.) 2*:210-16, 1959.
26. Sacher, G. A. Discussion of Kohn's and Comfort's essays, *Radiat. Res. (Suppl. 1)*: 241, 1959.
27. Rust, J. H. and others. Effects of 50 roentgens and 25 roentgens fractional daily total-body gamma irradiation in the burro, *Radiat. Res. 2*:475-82, 1955.
28. Trum, B. F., Shively, J. N., Kuhn, U. S. G. and Carll, W. T. Radiation injury and recovery in swine, *Radiat. Res. 11*: 326-42, 1959.
29. Upton, A. C., Wolff, F. F., Furth, J. and Kimball, A. W. Comparison of the induction of myeloid and lymphoid leukemias in x-radiated RF mice, *Cancer Res. 18*:842-48, 1958.
30. Kaplan, H. S. and Brown, M. B. Development of lymphoid tumors in non-irradiated thymic grafts in thymectomized irradiated mice, *Science 119*: 439-40, 1954.
31. Bierman, H. R., Kelly, K. H. and Cordes, F. L. Sequestration and visceral circulation of leucocytes in man, *Ann. N.Y. Acad. Sci. 59*:850-62, 1955.
32. Kohn, H. I. and Guttman, P. H. Letter in *Nature 184*:735-36, 1959; refer Kohn, H. I. Late effects of ionizing radiation, *Radiat. Res. (Suppl. 1)*: 235-42, 1959.
33. Lorenz, E. and others. In: *Biological Effects of External X- and Gamma Radiation*. R. E. Zirkle, edit. New York, McGraw-Hill, 1954, pp. 24-39.
34. Carlson, L. D. and Jackson, B. H. Combined effects of ionizing radiation and high temperature on the longevity of the Sprague-Dawley rat, *Radiat. Res. 11*:509-19, 1959.
35. Kallman, R. F. and Kohn, H. I. Life shortening by whole- and partial-body x-irradiation in mice, *Science 128*:301-02, 1958.
36. Kohn, H. I. and Zippin, C. Survival curves in cancer of the breast. *AEC Radiological Laboratory Report UCSF-19*:38-39, 1959.
37. Newell, R. R. Correlation of integral radiation dose with longevity in women cured of cervix carcinoma, to be published in *Proc. Ninth Int. Congr. for Radiology, 1959.*
38. Newell, R. R. and Cronkite, E. C. Can statistics mislead? *Stanf. med. Bull. 8*. 51-52, 1950.
39. Newell, R. R. Human tolerance for large amounts of radiation, *Radiology 54*:598-601, 1950.
40. *Panel discussion.* (See ref. 6), pp. 628-35.
41. Seltser, R. and Sartwell, P. E. Ionizing radiation and the longevity of physicians, *J. Amer. med. Assoc. 166*:585-87, 1958.
42. Lewis, E. B. Leukemia and ionizing radiation, *Science 125*:965-72, 1957.
43. Court-Brown, W. M. and Doll, R. Leukemia and aplastic anemia in patients irradiated for ankylosing spondylitis, *Med. Res. Counc. Special Rep.*, Series No. 295, London, 1957.
44. Lamerton, L. F. Examination of the clinical and experimental data relating to the possible hazard to the individual of small doses of radiation, *Brit. J. Radiol. 31*:229-39, 1958.
45. Loutit, J. F. Effects of radiation on the individual, *Practitioner 181*:553-58, 1958.
46. Brues, A. M. Critique of the linear theory of carcinogenesis, *Science 128*: 693-99, 1958.
47. Haenzel, William, Marcus, S. C. and Zimmer, E. G. Cancer morbidity in urban and rural Iowa, *Publ. Hlth. Monogr. No. 37*, U.S. Publ. Hlth. Serv. Publ. No. 462, 1956.

48. Grodewitz, William and others. Cancer illness among residents of 10 U.S. cities, Cancer Morbidity Ser. 8, Publ. Nos. 65, 67, 112, 126, 128, 152, 216, 217, 244, *U.S. Natl. Cancer Inst., Publ. Hlth. Serv.*, 1951-52.

49. Kaplan, J. G. Letter, *Science 130:*728-30, 1959.

50. Mays, C. W. Letter, *Science 130:*1600, 1959.

51. Moos, C. Letter, followed by letters from Dunn, L. C., Dobzhansky, T., and Finkel, M., *Science 128:*1532-34, 1580-82, 1958.

52. Björnerstedt, R. and Engström, A. Maximum permissible body burden of Sr^{90}, *Science 129:*327-28, 1959.

53. Björnerstedt, R. and Häggroth, S. Determination of Sr^{90} distribution in human bone, *Nature 185:*366-67, 1960.

54. Finkel, M. Late effects of internally deposited radioisotopes in laboratory animals, *Radiat. Res. (Suppl. 1):* 265-79, 1959.

55. Finkel, M. P. and Biskis, B. O. Induction of malignant bone tumors in mice by radioisotopes, *Acta Un. int. Cancr. 15:*99-106, 1959.

56. Jones, A. Irradiation sarcoma, *Brit. J. Radiol. 26:*273-84, 1953.

57. Cruz, Miguel, Coley, B. L. and Stewart, F. W. Postradiation bone sarcoma: report of eleven cases, *Cancer 10:*72-88, 1957.

58. Rowland, R. E. and Marshall, J. H. Radium in human bone, *Radiat. Res. 11:*299-313, 1959.

59. Finkel, M. Mice, men and fallout, *Science 128:*637-41, 1958. *Ibid.*, Letter, 1534, 1580-82, 1958.

60. Maximum permissible body burden and maximum permissible concentrations in air and water for the several radioactive nucleides, Natl. Comm. on Radiation Protection, *Handb. Ser., U.S. Bur. Stand. No. 69*, U.S. Govt. Pr. Off., 1959. (All the handbooks are listed inside the cover. HB76 will soon replace HB60.)

61. Simpson, C. L. and Hempelmann, L. H. Association of tumors and roentgen-ray treatment of the thorax in infancy, *Cancer 10:*42-56, 1957.

62. Rooney, D. R. and Powell, R. W. Carcinoma of the thyroid in children after x-ray therapy in early childhood, *J. Amer. med. Assoc. 169:*1-4, 1958.

63. Stewart, A., Webb, J., Giles, D. and Hewitt, D. Malignant disease in childhood and diagnostic irradiation in utero, *Lancet 2:*447, 1956.
Stewart, A., Webb, J. and Hewitt, D. Survey of childhood malignancies, *Brit. med. J. 1:*1495-1508, 1958.

64. *Rep. of U. N. Scientific Comm. on Effects of Atomic Radiation, Suppl. 17 (A/3838)*, New York, 1958, pp. 61-97.

65. Scott, W. G. The Emergence of the clinical radiologist and his problems, *Amer. J. Roentgenol. 78:*939-43, Dec. 1957, followed by essays on protection by E. Quimby, G. Failla, P. McClement, B. Glass, J. S. Laughlin, L. S. Taylor, C. B. Braestrup, R. S. Stone and summary by R. S. Chamberlain.

66. Lincoln, T. A. and Gupton, E. D. Radiation doses in diagnostic x-ray procedures, *Radiology 71:*208-15, 1958.
Reinsma, I. K. Evaluation of the integral absorbed dose in diagnostic roentgenology, *Medicamundi 5:*41-46, 1959.

67. Norwood, W. D. and others. Gonadal radiation dose received by the people of a small American city due to diagnostic use of roentgen rays, *Amer. J. Roentgenol. 82:*1081-97, 1959.

68. Newell, R. R. and Briggs, R. Cholecystography: optimum voltage, *Radiology 34:*568-70, 1940.

69. See ref. 5, p. 115.

70. Pauling, L. Genetic and somatic effects of C^{14}, *Science 128:*1183-86, 1958.

71. Totter, J. R., Zelle, M. R. and Hollister, H. Biological hazard to man of Carbon-14 from nuclear weapons, *Wash-1008, U.S. Atomic Energy Comm., Div. Biol. Med.*, 1958, pp. 1-19.

COMMON UROLOGICAL PROBLEMS IN GENERAL PRACTICE

*Transcription of a Panel Meeting on Therapeutics**

VICTOR F. MARSHALL . . . Moderator

Professor of Clinical Surgery (Urology), Cornell University Medical College; Attending Surgeon in Charge of Urology, The New York Hospital

Panel Members

SIMON A. BEISLER

Chief, Department of Urology, Roosevelt Hospital, New York

FRANK C. HAMM

Professor of Urology, State University of New York, Downstate Medical Center; Director, Department of Urology, Brooklyn Hospital

RALPH J. VEENEMA

Assistant Attending Urologist, Columbia-Presbyterian Medical Center; Associate in Urology, College of Physicians and Surgeons, Columbia University

* Presented at the Monthly Panel Meeting, Sixth Series, at The New York Academy of Medicine,

MODERATOR MARSHALL: The topic for discussion this afternoon is "Common Urological Problems in General Practice". However, we shall not try to cover every facet of urology that might be met in general practice, but we have selected certain topics which we thought would interest you. The first item which we have selected for consideration is the treatment of hydrocele. As you all know, hydrocele is a rather common disorder, often seen in infants at the time of birth. *Dr. Beisler, which types of hydrocele do you think do not require any treatment?*

DR. SIMON A. BEISLER: The scrotal hydrocele noted at birth or in early infancy should be observed rather than immediately subjected to surgery, because many will disappear in the course of a month or two.

MODERATOR MARSHALL: *How about in adults?*

DR. BEISLER: That is a horse of a different color. In the adult, I think a fair-sized hydrocele which causes some difficulties because of its weight is best managed surgically. If it is a small hydrocele not causing symptoms, there is no need to do anything.

MODERATOR MARSHALL: *Do you think a large and tense hydrocele in a young man has any effect on his powers of spermatogenesis?*

DR. BEISLER: I doubt it.

MODERATOR MARSHALL: *Dr. Hamm, do you think it has anything to do with his ability to produce sperms?*

DR. FRANK C. HAMM: No.

MODERATOR MARSHALL: Dr. Veenema?

DR. RALPH VEENEMA: I do not.

MODERATOR MARSHALL: I asked that question because I have seen a few patients with good-sized hydroceles who were anxious to have the hydrocele corrected in order to preserve fertility. There are, of course, other reasons for treating hydroceles. I think fertility is rarely, if ever, impaired by simple hydrocele. No one knows whether the rarely encountered, large, and extremely tense hydrocele of infants can cause sterility—this may be possible but seems unlikely. How should you treat a hydrocele that warrants therapy? Let us assume the hydrocele is large, heavy and in the way, and requires treatment. Most patients would prefer to have a little needle put into it and thus end the problem. *This is the question: aspiration versus operation. Dr. Hamm?*

DR. HAMM: Aspiration is all right, but the sac begins to fill up almost as soon as it has been evacuated, so that within a few weeks one is again faced with the same problem. Generally speaking, I favor operation. It

is quite a simple thing to do surgically. What one does is to evacuate the sac, resect the redundant portion and turn it inside out, and take a couple of stitches in it.

MODERATOR MARSHALL: *If one is prepared to aspirate it, should there not be a word of caution about making sure that it is a hydrocele and not a hernia?*

DR. HAMM: Yes, and in addition, some hydroceles communicate with the peritoneal cavity. I should also point out that the injection treatment is not always satisfactory. It is extremely painful and the injection of a sclerosing solution may result in a painful indurated nodule in or about the testicle which may give the patient as much or more trouble than he had originally.

MODERATOR MARSHALL: *Indeed, may not the injection treatment be more painful than the removal of the tunica vaginalis?*

DR. HAMM: I would think so.

MODERATOR MARSHALL: It is not unusual for the young man to appear saying that he is trying to get onto a police force or a fire department and has been advised to have an asymptomatic varicocele corrected. *Dr. Hamm, just how serious is a varicocele? What does it lead to?*

DR. HAMM: In my experience it doesn't really lead to anything. A moderate-sized varicocele is a very common thing, occurring on the left side. If it occurs on the right side it may be a sign of serious disease; namely, malignancy of the right kidney. But with the ordinary varicocele which occurs on the left side, I am inclined to pass it over, not to advise any surgery unless it is of enormous size.

MODERATOR MARSHALL: It is well known that some champion athletes have quite obvious varicoceles that do not bother them significantly. *Do you think it has any effect on sexual ability, particularly the production of sperm?* Every once in a while it is stated that patients who have varicocele seem to have a higher than normal incidence of small testicle on that side.

DR. HAMM: I don't believe it affects spermatogenesis.

MODERATOR MARSHALL: *Dr. Beisler, do you think it affects spermatogenesis?*

DR. BEISLER: No, I don't think so. As you said, occasionally one will encounter quite a small testicle on the side where there is a very large varicocele, but as long as there is compensation on the right side I don't believe the question of fertility will arise.

MODERATOR MARSHALL: *Dr. Hamm, how would you treat the varicocele, if there is some reason for doing so? If the patient wants to get into a fire department, for example, do you consider that an adequate indication for treatment of the varicocele?*

DR. HAMM: If it is a hard and fast requirement, I think it is quite all right to operate. In the ones I have done recently I have simply ligated the spermatic vein. I have not attempted to dissect out all the ramifications of the varicocele.

MODERATOR MARSHALL: Dr. Lloyd Lewis and Dr. Carl Javert have been in favor of that type of operation. *Dr. Veenema, what technique do you use?*

DR. VEENEMA: I approach it through an inguinal incision, and ligate the internal spermatic vein at the internal inguinal ring. If the varicocele is large, and such an occasion has arisen recently with some young Air-Force men who were asked to have it done before they were accepted into the Corps, I dissect out some of the large vessels in order to avoid the possibility of painful thrombi forming in them. I think that is rather immaterial, but it might result in a little better cosmetic result.

MODERATOR MARSHALL: It just occurs to me that, in this age of jets, and rockets, a varicocele might perhaps be of significance in a pilot subject to tremendous gravitational and centrifugal forces. *Maybe he would develop some kind of thrombosis or hemorrhage. I know nothing about it. Do any of the rest of you?*

DR. BEISLER: No.

DR. VEENEMA: I know that the Air Force has required that the operation be done in some of the younger men who have applied for admission from various ROTC groups. They were rejected until they had the varicocele repaired. This is a somewhat different attitude than most of us were accustomed to in previous army duty, where varicoceles were usually ignored.

MODERATOR MARSHALL: I take it that the panel feels quite conservative about varicoceles in general. It is not a serious matter, except perhaps for the anxiety the patient may have about it. The main treatment is mostly reassurance, if necessary, and active treatment depends on its necessity for getting a job. A really huge varicocele is not common.

I suppose that nearly every physician sees patients with cryptorchism. If he does not see such patients, he always has some friends who know of a child with the condition. The first item for consideration

is, of course, the diagnosis. Not every testis that is supposed to be undescended is truly undescended. *How can you be sure that a testis is really undescended, not one that just retreats easily?*

DR. BEISLER: That may involve seeing the child more than once. If on examination the testis is ever found down in the scrotum, even though it later disappears from time to time, it will eventually come down and remain down.

MODERATOR MARSHALL: *You would not be inclined to resort to hormones, let alone surgery, in such a case?*

DR. BEISLER: I would not do anything at all for that youngster.

MODERATOR MARSHALL: *If you are not able definitely to identify the testis or, though able to feel it, you cannot push it down into the scrotum, what further procedures do you do?*

DR. BEISLER: I personally am rather conservative in the treatment of these testes. If I can't push the testis down, and if I feel that it has an attachment at its gubernaculum so that it is "flopped over", I don't think anything will bring it down but surgery. But if the testis cannot be felt at all, that is a different matter, and that is where some disagreement enters the picture. Some people favor getting after that testis early, with massive doses of anterior pituitary-like hormone, and seeing what this may accomplish. But very few of them will come down, and if massive doses of the hormone fail to induce descent, surgery is resorted to.

MODERATOR MARSHALL: Dr. Beisler mentioned the testis that is "flopped over". That may not be altogether clear. I think he is referring to the testis which does come out of the external inguinal ring but instead of descending into the scrotum, it bends back up on the abdominal wall. It is really a partially ectopic testis, as well as an undescended one. Such testes are usually partly fixed in position, and they will not be made to descend by any treatment other than surgery. *Is it that kind of case you were referring to?*

DR. BEISLER: That is right.

MODERATOR MARSHALL: It is important to realize that this is a rather common peculiarity. It appears to be an undescended testis, whereas, strictly speaking, it should be considered an ectopic testis. The cord is fairly long and the surgical results in this situation are quite good.

At what age should patients with cryptorchism be treated? Shall we begin to treat them when born? Shall we wait until they are at

puberty? I think everybody agrees that to wait until after puberty gives poor results. *At what age would you electively treat a child with an undescended testis, Dr. Veenema?*

DR. VEENEMA: This is a very controversial point, but it seems to me that, although tradition favors the 9 to 11 age group for treatment, the evidence that has been accumulated favors earlier intervention. This evidence is based on studies of the growth of the normal testis by Sniffen and the studies of Dr. Robinson and Dr. Engle, in which they biopsied both the unilaterally undescended testis and the testis that was descended. Biopsies of bilaterally undescended testes in various age groups were also done. Generally speaking, both the descended and the undescended testes follow a parallel growth phase up to about the age of five years. After the age of five, the descended testis histologically appears to go on to a normal development, while the undescended testis appears to remain in a retarded growth phase. On the basis of this evidence, we at Columbia-Presbyterian feel we should intervene earlier in these cases and operate, or at least clarify the undescended testicle status of the patient, somewhere between the ages of five and seven years. We prefer that these patients be evaluated earlier than age 9 to 11. If we hope to preserve fertility in these testes, we should favor earlier intervention. Whether these undescended testes are inherently inferior is an important question. Perhaps we are attempting to salvage something of no value. Much more study needs to be devoted to this problem.

MODERATOR MARSHALL: It is rather surprising how little is actually known about this common problem, but there does seem to be a definite trend to take active measures on these undescended testes at a much earlier age than formerly. *Does the panel agree with Dr. Veenema?*

DR. HAMM: Yes, I agree. I think we should start treating these patients earlier than we have in the past and I believe five years seems to be the proper age.

MODERATOR MARSHALL: There is some good evidence that the undescended testis does drop behind the good testis in developmental progress at about the age of five. Dr. Beisler?

DR. BEISLER: As a group, yes.

MODERATOR MARSHALL: We have a question which says: *What would you do with the small migrating testis? How long would you wait before starting therapy, and would you use hormones? Dr. Beisler, you touched on that subject?*

DR. BEISLER: I assume from the term "migrating testis" that, at times, the testis is felt within the scrotal sac and at other times outside the scrotal sac. With that type of testis I would wait for quite a period of time. If it persisted to about age 7 or so, it would not do any harm to try a course of the anterior pituitary hormone, noting what effect the hormone has on increasing the size of the testicle. But I still would not operate on that child until later, because I think many of them will, about the age of 11 or 12, descend and remain down.

MODERATOR MARSHALL: You imply that some do not. *Do you think about 95 per cent will actually come down?*

DR. BEISLER: I should estimate it at 95 to 98 per cent.

MODERATOR MARSHALL: Dr. Veenema, do you feel the same way?

DR. VEENEMA: I believe the migratory testis is considerably different from the truly undescended or ectopic testis. If we find a migratory testis, we like to give a course of hormone treatment and see if the problem can be somewhat clarified. I feel one has nothing to lose by giving the patient the APL hormone, a total of about 20,000 units, to see if that therapeutic test is effective.

MODERATOR MARSHALL: One of the great advantages of using hormones in the treatment of the migrating testis is that it will raise the percentage of success! At least, most of the testes which descend following hormone treatment are of the migrating type. Hormones may also be helpful by increasing the size of the testis so that it may be more readily identified, particularly in fat little boys.

Now, the question of hormones versus operation. *Dr. Veenema, should hormones always be given? Are hormones more, or less effective than operation?*

DR. VEENEMA: I think we have touched on that already. As you have said, it does no harm to have the testis increase a little in size and this gives a better opportunity at operation for identification in some of these fat boys. The hormone injections may also clarify some cases about which one might be in doubt as to whether one is really dealing with a migratory testis. All migratory testes are not clearly identified and perhaps, after giving a course of hormones, one may change his mind about the case and not operate at all, since the testis may have progressed downward and is perhaps almost ready to drop into the scrotum. The reported results with the use of hormones, as Dr. Marshall has said, do vary considerably, all the way from zero per cent to 90

per cent effective. But we think that they are helpful in clarifying the status of the patient with undescended testis.

MODERATOR MARSHALL: *More as a diagnostic measure than a purely therapeutic effort?*

DR. VEENEMA: Yes.

MODERATOR MARSHALL: You mentioned earlier that some of these testes may be inherently defective, and for these we may not be able to accomplish much with any form of treatment. *Can you tell which ones are inherently defective?*

DR. VEENEMA: As we all know, some of them are very small, pea-sized, and those, I think we would all readily agree, are of no value to the patient. But at operation a testis may appear fairly normal even though slightly smaller than normal in size. I don't think one can tell much about these on gross examination. Examined microscopically, the undescended testis may present a picture varying from complete germinal aplasia to showing a moderate number of spermatogonia. I believe one has to depend on histological evidence to tell whether they are inherently poor.

MODERATOR MARSHALL: Would you be willing to make a guess as *to what percentage of the undescended testes, not migratory testes, are inherently of little value; that is, even if you succeed in bringing them down, would they be able to produce sperm to any useful degree?*

DR. VEENEMA: You ask for a guess, and I would say that probably all of the truly undescended testes are of little value, as far as sperm production is concerned.

MODERATOR MARSHALL: *Dr. Hamm, do you feel the same way about it?*

DR. HAMM: No, I don't think that. I don't take quite as dim a view as that. I think many of them *are* defective, of course. The exact figure remains to be determined.

MODERATOR MARSHALL: The picture has certainly dimmed in recent years. It was glibly thought a few years ago that we could routinely produce excellent results if these testes could be satisfactorily placed in the scrotum. A significant number of these testes are inherently deficient, and at present we don't know anything that can be done to restore these testes to normal function. It is obvious, of course, that one can distinguish a few of these deficient testes in advance. But as Dr. Veenema pointed out, there are a goodly number of these which, under

direct vision and on palpation in the operating room, appear essentially normal, yet are predetermined to have poor prognosis, even though a technically successful operation is accomplished. I agree that a lot more study is needed in this area.

Dr. Hamm, what results are to be expected from operating on the undescended testis?

DR. HAMM: I think that the best results are, without question, obtained with surgery. I wish also to mention some of the evils associated with long-continued medical treatment, such as precocious puberty, hypertrophy of the genitalia, and premature closure of the epiphyses. I don't think medical treatment should be continued over a long period. I believe one course of medical treatment is enough.

MODERATOR MARSHALL: The other question is: Which undescended testes should be removed? We hear a great deal about the higher incidence of cancer in the undescended one. Some difference of opinion exists about this, but it seems that almost everyone who studies it from the statistical point of view comes around to the view that cancer is more common in undescended testes than in normally descended ones. Dr. Hamm, which of these undescended testes would you remove forthwith?

DR. HAMM: Fortunately, we are not faced with this problem too often, but when we are, it is extremely important to make the proper decision. I remove a testis when it is so highly situated up in the abdomen that the possibility of returning it to its normal position in the scrotum is obviously nil; but even then I remove it only when there is a normal one on the opposite side. In other words, I don't believe we are justified in castrating the child, even though the testis is very defective and likely to become diseased later on.

MODERATOR MARSHALL: *Do other members of the panel have the same general feeling about removing the testicle?*

DR. BEISLER: Yes.

DR. VEENEMA: Yes.

MODERATOR MARSHALL: A certain number of these children are obese and in appearance somewhat resemble those with the Fröhlich syndrome. *Would you treat them any differently, Dr. Beisler?*

DR. BEISLER: I have been much impressed with the results obtained in these children by a combination of thyroid extract by mouth and anterior pituitary extract parenterally. The effect is not only in the

descent, in the development of the testis, but in the whole general appearance of these children, which is greatly improved by the therapy.

MODERATOR MARSHALL: The next subject for discussion is enuresis. The parents say their child wets the bed. The first question one usually asks is: How old is he (or she)? So it would seem that enuresis, without other associated signs or symptoms, is normal up to some age. *Normal up to what age, would you say?*

DR. BEISLER: It is fairly well accepted as being normal up to about the age of five or six years.

MODERATOR MARSHALL: *How concerned would you be if the child were seven or eight?*

DR. BEISLER: I would be somewhat more interested. Then, I would think in terms of a urological survey, intravenous pyelograms, cystourethroscopic examination.

MODERATOR MARSHALL: *In other words, if the child had enuresis at the age of eight and nothing else to go with it, you would be willing to do, in addition to the urinalysis and general physical examination, an intravenous pyelogram?*

DR. BEISLER: Yes.

MODERATOR MARSHALL: *Dr. Veenema, what considerations would cause you to do an intravenous pyelogram in a child with enuresis who was less than eight years of age?*

DR. VEENEMA: The child that has enuresis complicated by pyuria, some urinary dribbling and frequency during the day. I would also consider intravenous pyelography for the child who has a small urinary stream or where, on physical examination, a small external meatus and a changing pattern in voiding has been noted. Another important problem is the child who has been all right for a year or two and then begins to be enuretic again. I think the main thing is to look for pus in the urine; even a small amount may be significant.

MODERATOR MARSHALL: Dr. Hamm, do you feel about the same as the other members of the panel?

DR. HAMM: I do. I had an opportunity to examine several hundred adult males in the army who had enuresis. As you know, the army takes a dim view of these men, because it is difficult for them to live in the same barracks with other soldiers. I more or less came to the conclusion that it represented a fairly definite syndrome, with a familial tendency. Their urinary symptoms were aggravated under stress. The closer they

got to the battle front, the more frequency they had. Under stress, frequency is common with almost everyone, but some of them became actually incontinent. I think there is another psychic aspect to enuresis too, and that is that practically all of the young men I examined were very deep sleepers. They gave the story that it was almost impossible for them to be awakened during the night.

MODERATOR MARSHALL: *How frequently did you find organic urological disorders in the army group that had enuresis? How often did you find hydronephrosis, serious anomalies, bladder obstructions?*

DR. HAMM: I found them rarely. It was very uncommon to find any organic urologic condition to account for the enuresis.

MODERATOR MARSHALL: I would gather that the panel agrees that most enuresis is on a psychological or habit basis. When it is not on that basis, there is usually something else to be found, something in the history about how he voids or some abnormality to be found in the urine. After the age of six or seven years, one would begin to think about the possibilities of some significant organic urological disorder.

What should one do with a child who has some pus in the urine? Should there be a mere dosing of the patient with some fashionable drugs? Should one "match the drugs and bugs" to make it still more scientific? Or, should we really examine the patient and, if so, to what extent? All of this has a fundamental bearing on the causes of pyuria in childhood. *Dr. Beisler, what would you say, in broad terms, is the cause of pyuria in childhood?*

DR. BEISLER: In repeated pyurias one would suspect some type of mechanical obstruction somewhere in the urinary tract, the common ones being those found at the uretero-pelvic junction, either a congenital stricture or an aberrant blood vessel with some congenital bands. Other sites of obstruction might be constriction at the uretero-vesical junction, a median bar of the bladder, the urethral valves and, in some instances, a small external meatus.

MODERATOR MARSHALL: *But these are really congenital obstructive disorders?*

DR. BEISLER: That is correct.

MODERATOR MARSHALL: This would be in contradistinction to adults, in whom cancers and stones would be quite common causes, as well as obstructions. You indicate mechanical obstructions. *What about the neurogenic bladders, or any other neurogenic dysfunction in the*

urinary tract? It has been suggested that congenital localized neurogenic dysfunction is common.

DR. BEISLER: The neurogenic type is usually associated with an acquired rather than a congenital median bar, and to me they are both somewhat on a par. Even if it is of neurogenic origin, something can probably be accomplished by a resection of the bar, with or without a Y-V plastic procedure on the anterior aspect of the bladder neck.

MODERATOR MARSHALL: I have been much interested in this problem, because every time the bladder does not function properly, and no lesion can be demonstrated and no definitive diagnosis can be made, somebody invariably tags it as "neurogenic". In effect, they challenge you to say it is not so, and they have the better of the argument because they said it first! I think that the number of supposedly neurogenic bladders is gradually decreasing. More and more are being recognized as being due to mechanical obstruction, as Dr. Beisler has said. Considerably fewer of them have authentic idiopathic types of neurogenic bladders. However, truly neurogenic bladders do occur. *Dr. Veenema, how do you know a disorder is that of a neurogenic bladder?*

DR. VEENEMA: By the process of elimination, sometimes! Also a neurological consultant may help considerably, but often he will say the only neurological defect he can find is that which is evident in the bladder. Then you are right back where you started!

MODERATOR MARSHALL: *And you accept his opinion?*

DR. VEENEMA: If there is absence of pain and temperature sensation in the bladder, that is pretty good evidence to indicate that the patient does have some neurogenic element to his bladder dysfunction. I personally feel that the large majority of them are bladder-neck mechanical obstruction. As far as the bladder itself is concerned, one has to depend upon the presence or absence of pain and temperature sensation and cystometric studies.

MODERATOR MARSHALL: *Dr. Hamm, don't you think it is really quite rare for a patient, old or young, to have truly neurogenic malfunction of the bladder when, after a complete neurological examination has been done, there are no other positive neurological findings? The examiner finds normal tonus of the anal sphincter, normal sensation in the perineum and normal reflexes in the legs, etc., and the patient has no history of neurological disease?*

DR. HAMM: I do.

MODERATOR MARSHALL: I think it is extremely rare. Whenever a patient is seen who has been diagnosed as having a neurogenic bladder, yet who shows no evidence of neurological abnormality elsewhere in the body, one had better believe that the bladder dysfunction is not neurogenic in origin. I believe we are agreed on that.

We have another question: *Is there any limitation to matching drugs and bugs?* There is no limitation to matching the drugs and bugs ad infinitum, even unto the death of the patient, a result of failure to take the proper measures. As has been pointed out, the underlying condition in these children is the obstruction in the urinary tract. Although they may live a little longer by suppressing the infection with these marvelous modern drugs, they can still die, with and without sterile urine. These drugs tend to become less effective as time goes on, time during which the obstructive effects become greater. I personally feel that far too much drug matching is done. I present a little girl with pyuria to a class of medical students. One of the first questions will be: "What organism is present?" If I happen to know, the student recalls to mind a drug manufacturer's chart showing common sensitivities—and promptly and optimistically prescribes. No more diagnosis, just treatment! This is very dangerous.

At what point should a child with pyuria be referred for detailed investigation, Dr. Veenema?

DR. VEENEMA: I think that we have answered this in some of our previous statements, and I would agree about the limitations of matching the drugs and the bugs. If the child does not respond promptly to a rather broad spectrum antibiotic, one should look for urinary tract obstruction and not waste time for the patient. I think too many of them go on too long with recurrent episodes. As a rule of thumb, if episodes recur even once, it is good to have them properly evaluated by adequate investigation.

MODERATOR MARSHALL: The next subject for discussion is hematuria. A study of 1000 cases of gross total hematuria has been published by Davis and Lee. They showed that in these 1000 cases some 22 per cent were caused by the presence of cancer in the urinary tract. The incidence of other diseases varied tremendously, infections of one kind or another were very high, but approximately 80 to 90 per cent of the patients had a serious disorder.

Dr. Hamm, how would you localize the source of a hematuria? A

patient comes in your office and says, "I have blood in the urine". You take a history. *How do you go about finding out where this blood is coming from?*

DR. HAMM: The history is important. I think one should ask the patient: Does the blood appear at the beginning of urination? That suggests there may be some lesion around the bladder neck. Then one might ask: Does it appear at the end of urination? This usually suggests an inflammatory condition of the bladder with ulceration, in which the bladder expels a drop or two at the end of micturition. Or does the blood appear throughout the act of urination, which implies that there may be a lesion in the bladder or kidneys.

MODERATOR MARSHALL: *If the patient voids and you see that he has indeed blood in his urine, what would you do further?*

DR. HAMM: It is extremely important to investigate the cause of the bleeding and to try to localize the source without delay. If you can look into the bladder with a cystoscope and actually see the blood coming from one ureteral orifice, I think you have made a great advance in arriving at your diagnosis.

MODERATOR MARSHALL: That is the reason I asked the question. It is well to know, and to keep in mind, that bleeding does not necessarily continue. If the urine is dark enough, so that one can see the colored fluid coming from one or the other of the ureteral orifices, it is best to seize the opportunity to see where it comes from. The bleeding may stop and then it may, at least temporarily, be too late to determine the source. If the blood is seen coming from one ureter, and indeed sometimes from both ureters, this information is of solid major importance. Gross hematuria is, in my opinion, one of the few indications for an emergency observation cystoscopy.

Dr. Beisler, do you know of any good pills to stop the hematuria?

DR. BEISLER: That would be the last thing I would give a patient! I would want to have a thorough study of the entire genito-urinary tract.

MODERATOR MARSHALL: *Do you think the hematuria might very well stop after some pills?*

DR. BEISLER: It stops without pills, so it probably would stop with them!

MODERATOR MARSHALL: Amen!

Our next topic is that of "lumps in the prostate". The alert, careful

examiner should put his finger in every orifice that will accommodate it, and among the things he should be feeling is the prostate. Suppose he feels a lump in the prostate. *What are the causes of these lumps, Dr. Beisler?* If the causes are not very important, there is not much point in examining the prostate.

DR. BEISLER: A common cause would be that occasionally seen in a patient with a stone of appreciable size, or multiple smaller stones that may be felt, with or without crepitation. Of course, if crepitation is noted, that solves the problem of diagnosis. One will occasionally see a patient who has tuberculosis of the prostate. That is not very common these days. There is also the patient who has an acute inflammatory condition, often localized to one lobe of the prostate, which makes quite a difference in the feel of one side or the other. Those experienced in palpating the prostate may be able to recognize it as an induration, but they, too, have been known to fail. Also, one may discover an accessory lobule of the prostate which is a benign lesion, and, of course, most important of all, is carcinoma of the prostate.

MODERATOR MARSHALL: *Dr. Hamm, if you find a lump in the prostate which you suspect may be a carcinoma, how would you confirm the diagnosis?*

DR. HAMM: I would first obtain an x-ray to eliminate the possibility of stone. To rule out tuberculosis, one should examine the urine very carefully, because the presence of just a few leukocytes in the urine may be a clue. The examination of the prostate should, of course, be done meticulously and should always be done in pretty much the same way; for example, the bladder should always be empty, because it gives a false impression of the size of the prostate if the bladder is filled. Also, it is always advisable to have the patient in the same position. I usually have ambulatory patients standing on the floor and leaning over the bed.

MODERATOR MARSHALL: *How about x-rays of areas other than that of the prostate? Are there any blood tests that you might have done?*

DR. HAMM: One might want x-rays of the long bones, lower spine and pelvis, because in some instances carcinoma of the prostate may metastasize quite early. In addition, one would want to have a serum acid phosphatase determination.

MODERATOR MARSHALL: Those are the principal things. The chest plate will occasionally show something; and it also is advisable to palpate the nodes in the neck. But now, we have done all these things, yet we

find no evidence that the suggested cancer has spread beyond the prostate. *Dr. Veenema, how shall we proceed?*

DR. VEENEMA: The palpating finger is the best screen for evaluating prostates. After we have found a suspicious area, then the burden of proof rests with us as physicians to identify this area, whether stone, chronic inflammation, or cystic dilated acinus of the prostate, and, actually, the only way that it can be identified is by biopsy. Even if stone is visible by x-ray, there still may be carcinoma present in the prostate. In some octogenarian who has a hard area in the prostate and is a bad medical risk, it may require considerable clinical judgment to decide how far one should go, but, as a general principle, to identify a nodule palpated rectally by the examining finger, we must biopsy it. In biopsying, we like to proceed first with a closed needle biopsy of the suspicious area. If that is positive on the permanent sections, then we are free to proceed with any approach to the prostate suitable for radical prostatectomy: either retropubic or perineal. If it is a prostate of a gentleman who is not agreeable to radical surgery, one can proceed with bilateral orchiectomy. If the needle biopsy is negative, it proves nothing. One should follow with the open perineal biopsy, with frozen sections and permanent sections for microscopic examination.

MODERATOR MARSHALL: There is no substitute for histological evidence that the patient has cancer before one decides on appropriate treatment except, perhaps, in the occasional patient who, for one reason or another, is a very poor risk.

DR. VEENEMA: I would agree.

MODERATOR MARSHALL: How about bloody ejaculates? Every once in a while a patient appears in the office and says he has had an ejaculation which is bloody or brownish. *How serious is this?*

DR. BEISLER: Until I talked with you the other night I did not think it was serious at all, and I think you ought to tell us about that.

MODERATOR MARSHALL: I have seen two examples of bloody ejaculation that did have some serious background. They would be two out of at least 50 giving a history of bloody ejaculation. One can nearly always find some evidence of prostatitis, but I refer to serious conditions. One of these patients had extensive pulmonary tuberculosis, so that TBC would be suspected if anything was not right in any other part of his body. We did prove eventually that he had tuberculosis in one kidney and in his prostate. The other patient had bloody ejaculations, and I

carried out three cystoscopic examinations before I finally saw that the blood always appeared when I pressed on the prostate, from one side of the prostate down the prostate ducts, and not from the other side. To make a long story short, he did have a carcinoma of the prostate which apparently originated within those ducts and was not palpable. There was, however, a little palpable asymmetry of the prostate. Actually, bloody ejaculation is a rather unusual sign, and even more unusual as a sign of serious disease. *Dr. Hamm, is that your impression too?*

DR. HAMM: I have not found any really serious disease in the patients I have observed.

MODERATOR MARSHALL: We have another question. Dr. Hamm said that varicocele on the right side is of more importance than when on the left side and, if I remember correctly, he pointed out that this might mean obstruction of the circulation on the right side, such as might be caused by a renal tumor or other retroperitoneal tumor. Then the question is: How about a case of situs inversus? Dextrocardia is said to be found as often as one in 8000 routine chest plates. Would that rule out the importance of the statement with regard to varicocele?

I did not know situs inversus occurred as often as that. I have seen only two such patients. *How many have you seen, Dr. Beisler?*

DR. BEISLER: No more than that.

DR. VEENEMA: A right-sided varicocele surely warrants an intravenous pyelogram.

MODERATOR MARSHALL: We now have a few questions submitted by members of the audience. *Please discuss the advisability of cystourethroscopy in enuresis. Dr. Hamm?*

DR. HAMM: Even though we have not found a large percentage of patients with genuine organic disease, I think the first step in working them up is to get a thorough urologic survey.

MODERATOR MARSHALL: *You start with what?*

DR. HAMM: Complete cystoscopy.

MODERATOR MARSHALL: *Not an intravenous pyelogram?*

DR. HAMM: I do the whole thing, including direct inspection through the cystoscope and pyelograms.

MODERATOR MARSHALL: The next question is: *How common is a sliding hernia, associated with a congenital hydrocele?*

DR. VEENEMA: I have not seen sliding hernias in association with hydrocele. Uusally, one can demarcate the hydrocele quite readily. I

should say it is very uncommon.

MODERATOR MARSHALL: *Dr. Beisler?*

DR. BEISLER: I don't think it is common.

MODERATOR MARSHALL: I don't believe it is very common either, but we must remember that this panel is composed of urologists. If there is a hernia, the general surgeons have probably worked on it from that point of view. I remember one in a child and one in a young man of 20 or so.

In cases where the testis atrophies after varicocele repair, how common is secondary infertility? Dr. Beisler?

DR. BEISLER: I assume that at the time of the repair, something happened to the spermatic artery on that side and that the testis would become incapable of spermatogenesis.

MODERATOR MARSHALL: *And if the other testis was a good one to start with?*

DR. BEISLER: If the other one was a good one to start with, he would still have sperm in the semen.

MODERATOR MARSHALL: *How does one go about studying and treating the loss of libido in men?* This is a common problem.

DR. HAMM: That is really a difficult question!

MODERATOR MARSHALL: Give us the answer in ten seconds!

DR. HAMM: We proceed on the assumption that loss of libido in a healthy man who isn't too old, is psychogenic until proven otherwise. The exceptions to that are, of course, traumatic lesions of the spinal cord or some other serious disease process interfering with the nerve supply. Also, if surgery is performed on the seminal vesicles, especially if they are removed, a man will not be able to have an erection but, so far as I know, those constitute the only real organic lesions that will cause inability to have an erection.

MODERATOR MARSHALL: Some years ago we received a substantial grant from one of the pharmaceutical companies that manufacture hormones to investigate this question. We set up an elaborate plan. We were going to study the effect of 17-ketosteroids, estrogens, etc., in patients who came complaining of impotence and loss of libido. We had neurological and endocrinological consultants. These patients had a general history taken and a complete physical examination, including cysto-endoscopy, examination of various urine specimens, and blood tests. One could almost always tell from the history and general physical

examination alone whether the trouble was organic or psychological. For example, one of the patients gave a history suggesting anxiety, but while talking to him it was noticed that one pupil was larger than the other. He had central nervous system lues. One patient with a chief complaint of impotence was later found to have advanced cancer. On inspection he did appear pale, and further investigation of his anemia led to the proper, complete diagnosis. Several of the patients came because they had had fractures of the pelvis and were subsequently unable to function sexually. One could readily detect that there was extensive disorder in the posterior urethra, with strictures, etc. It was very rare to miss a correct diagnosis after just a careful history and physical examination. We picked up a small number of neurological diseases, but we did not uncover a single causative endocrinological disorder except when it was first strongly suspected from the history and physical examination alone. We did *not* find patients who seemed to have male climacteric and similarly vague syndromes that one hears about, and for which various endocrine products have been recommended as treatment. We were unable to demonstrate these mild degrees of supposed hormonal imbalance as the true background, unless we include a few senile men with obvious arteriosclerosis.

It was of considerable interest that we did uncover a very significant number of serious psychiatric disorders. I remember during one week we saw two schizophrenics who had to be taken to Bellevue that same week. Most patients were anxious for various reasons and/or had established undesirable habit patterns. In short, the probability is very great that the patient's trouble is fundamentally psychological, if a simple history and physical examination have not indicated otherwise. *Would you agree with that, Dr. Beisler?*

DR. BEISLER: Yes.

MODERATOR MARSHALL: *What is the treatment of choice for urethral trichomoniasis in men, Dr. Veenema?*

DR. VEENEMA: It does occur, there is no question about that. A fair amount of it might be self-limiting. We treat it somewhat as we do any chronic prostatitis. There is a preparation, Tritheon, which is recommended for trichomoniasis. We have tried it in some patients but find it hard to evaluate its efficacy. Male trichomoniasis seems to subside spontaneously even without any treatment.

MODERATOR MARSHALL: Would you agree that the first thing to do

would be to be certain that his wife is examined and her infection, if any, is cleared up, so he won't be reinfected? *Would you use any particular drugs in his urethra? Would you douse it with a little silver nitrate or some fancy preparation?*

DR. VEENEMA: I don't think so.

MODERATOR MARSHALL: *Dr. Beisler, would you?*

DR. BEISLER: No, but I recall, and I think it was in this very room many years ago, when they had an evening on the treatment of the various conditions of the prostate, including trichomoniasis, and some members of the staff of one of our nearby institutions were talking about injecting various chemicals and dyes through the ejaculatory duct to clear up these infections. Dr. Pelouze of Philadelphia was present and took part in the discussion. You may remember him. Whenever he told anything it was in story form and always concerned a "friend" of his, and this "friend" had a trichomoniasis infection of his prostate, was constantly reinfecting his wife, and he had seen somebody else who had used all these things, and Pelouze said he did not know what to do about it. He sent the patient to the Department of Physiotherapy and there he was given six diathermy treatments per rectum, following which no further trichomonads could be found. On that basis I have treated several people with diathermy and it has seemed to be effective.

MODERATOR MARSHALL: We are getting near the end of our allotted time, but one other topic should be mentioned, and that is urethrotrigonitis in women. Nearly every one in general practice sees a certain number of women who have frequency and urgency. The urine is usually normal. The findings on pelvic examination may not help much. Sometimes there is slight tenderness when the bladder neck is palpated. The symptoms come and go. Peculiarly, the patient usually does not have to get up much at night. Cystoscopically there isn't much to be seen; a slightly bumpy-looking mucosa, a little congestion in the region of the trigone. These women are often labeled neurotics. *Dr. Hamm, do you think this is a neurotic manifestation?*

DR. HAMM: No, I don't. I think it is quite wrong that many of these women are referred to as neurotics because, in my experience, most of them have a definite disease.

MODERATOR MARSHALL: *What is the underlying pathologic lesion? If you could examine it under the microscope, what would you see and in what area?*

DR. HAMM: I believe that sections of the urethra in these conditions show a chronic inflammatory process and considerable fibrosis. Of course the urethra is also involved in the involutionary process of senile vaginitis. Most of us see these women at or past the menopause.

MODERATOR MARSHALL: *Dr. Beisler, would you outline a plan of treatment. How do you begin? For example, a patient comes to your office for the first time, without having had half a dozen things already tried. How would you go about treating her?*

DR. BEISLER: I would first determine what the bladder capacity is. This is usually done by using an ordinary catheter, with no more than a foot of gravity dilation. If the bladder capacity is found to be 10 ounces (300 ml.) or more, I would begin to use gradually increasing strengths of silver nitrate solution as a bladder irrigation, leaving a small amount of irrigating fluid in the bladder after removal of the catheter. If the urethra is snug and it does not readily admit at least a 24 Fr. sound, I would prefer to dilate that urethra gradually, and in the so-called postmenopause period I would try small doses of estrogen. Quite a few of them respond to this treatment.

MODERATOR MARSHALL: *How frequently do you treat them?*

DR. BEISLER: I usually treat them on a test period basis, preferably at intervals of about a week or ten days for about four or five times. If they show improvement during this time, and most of them do, I gradually increase the interval between treatments.

MODERATOR MARSHALL: *You did not make mention of sitz baths. Do you think they are useful?*

DR. BEISLER: I have not employed them.

MODERATOR MARSHALL: *Dr. Hamm, do you use the same general plan of approach?*

DR. HAMM: Yes. One should be on the lookout for interstitial cystitis. Dr. Beisler referred to that when he indicated that he prefers to test the capacity of the bladder. The interstitial type of cystitis usually has, of course, a normal urine. About the only way we can detect it is by testing the capacity. It is an extremely painful condition and produces marked frequency, both day and night.

MODERATOR MARSHALL: *Dr. Veenema, do you use any additional therapy in this non-specific urethro-trigonitis, which is so common?*

DR. VEENEMA: Our patients take a lot of sitz baths too. I think it is the patients who are really enthusiastic about sitz baths and emphasize

their importance. They are very comfortable after a sitz bath.

MODERATOR MARSHALL: *What other things would you mention as being worth using on these patients? Let us assume that the patient is better, but that a little more improvement is needed.*

DR. VEENEMA: Furacin urethral suppositories have been helpful in some patients, although some of them complain bitterly after they insert one, saying that it causes too much irritation. I think topical treatment such as that is helpful. Also if the patient is not responding at all to the treatment as outlined, and there is definite pathology at the bladder neck, it is necessary at times (but only very occasionally in our experience) to resort to transurethral resection of the polypoid or fibrosed neck of the bladder.

MODERATOR MARSHALL: *Does that transurethral resection ever result in any undesirable effects such as incontinence?*

DR. VEENEMA: Yes. It has to be done very carefully. Fistula can result and incontinence. We don't use it unless other more conservative treatment has failed.

MODERATOR MARSHALL: *Dr. Beisler, you agree that that is one of the things to do?*

DR. BEISLER: Yes, sir!

MODERATOR MARSHALL: I have one other thing in mind. I have, on occasion, used ophthalmic ointment in the urethra. Anything that can be put in the eye can be put in the urethra, it seems to me! Before Furacin suppositories became available I used to use regularly Aureomycin ophthalmic ointment as a soothing antiseptic. It seemed to help.

DR. VEENEMA: Dr. Marshall, I know our time is short but I would hate to have a panel on urology close without saying that in the patient with renal or ureteral colic an intravenous pyelogram is actually the only way to arrive at an accurate diagnosis. It is the only way to find the trouble, where it is located, and what it is doing to the kidney. Those are the three important things we have to know.

MODERATOR MARSHALL: Would anybody in the audience like to ask further questions? If not, we shall adjourn. I want to thank you all very much, and also to thank the members of the panel.

THE PLACE OF LUMBAR SYMPATHECTOMY IN THE LIGHT OF RECENT ADVANCES IN VASCULAR SURGERY*

FERDINAND F. MCALLISTER

In any field of medicine, as newer methods of treatment become available, it becomes desirable, from time to time, to reappraise the older modes of therapy. We have now had a decade of brilliant achievements in vascular surgery, characterized chiefly by the development of grafting techniques with a variety of blood vessel substitutes. Inevitably, there has been confusion as to the indications not only for the use of these techniques, but also for the use of the older and perhaps less effective weapons such as lumbar sympathectomy. As we have gained more experience with the grafting techniques, and as the long-term follow-ups have become increasingly disappointing, many of us in the field of vascular surgery have been forced to fall back upon and to reappraise lumbar sympathectomy. While some modern vascular surgeons continue to disparage it, there is little question that lumbar sympathectomy continues to be a valuable tool, provided one does not expect too much of it and provided one clearly understands its limitations.

The lumbar sympathectomy referred to is that employed by most of the surgeons at the Presbyterian Hospital consisting of the removal of the lumbar sympathetic chain including ganglia L_2, L_3 and L_4. In some more extreme instances L_1 and L_5 may be included.

There are three main aims of lumbar sympathectomy in occlusive arterial disease:

1. To improve skin nutrition so as to prevent or reduce ulceration.
2. To improve muscle circulation so as to ameliorate intermittent claudication.

* Presented at the meeting of the New York Surgical Society, held at The New York Academy of Medicine, December 14, 1960.

From the Department of Surgery, Presbyterian Hospital and the College of Physicians and Surgeons, Columbia University, New York City.

3. To improve the nutrition of peripheral nerves and to interrupt afferent impulses so as to modify ischemic rest pain.

No fancy tests or apparatus are required to determine whether one or more of these aims may be achieved in a given patient. However, some preoperative testing is essential, otherwise a host of unnecessary procedures may be performed. The simplest and perhaps the best way to produce a trial sympathetic blockade is by epidural anesthesia. Proper regulation of dosage will block only the autonomic and not the somatic nerves. A catheter may be inserted and the test repeated several times when the results are questionable. This prolonged blockade permits better evaluation, eliminates an objection that blocks of short duration do not permit sufficient time to allow for full vasodilatory effect and thus returns to an important position the role of preoperative testing. This has the further advantage of actively treating the patient over a considerable period.

Improvement in the color and temperature of the digits obviously indicates a beneficial result in the face of impending tissue necrosis. Where intermittent claudication is the reason for study, walking tolerance can be accurately measured before epidural block. If the patient can consistently walk further after block, it is reasonable to assume that sympathectomy will be helpful.

In the case of rest pain, relief of this following block, and in the absence of concurrent blockage of somatic pathways, indicates probable relief from sympathectomy.

Before considering specific indications and contraindications for sympathectomy, a few points are worth making. The first of these deals with intermittent claudication. There is a tendency now towards the belief that the only way to cure intermittent claudication is to reestablish continuity in the main artery. It should be emphasized in this respect that we have no assurance that reestablishing continuity in a main artery in any way arrests the progression of the disease process of atherosclerosis. In many instances the amount of surgery required for the reestablishment of continuity in a vessel is very extensive considering that it is done for the relief of the single symptom of claudication. It should be further emphasized that it is possible to relieve completely intermittent claudication by sympathectomy alone. Husni and Simeone[1] report 23 per cent of cases relieved of their claudication pain by sympathectomy. In my own cases, 17 per cent have been relieved of

claudication and over half have had improvement in walking power. DeBakey, Creech and Woodhall[2] report 85 per cent of cases improved where the problem was either intermittent claudication or ischemic neuritis.

The next point I would like to make relates to the concomitant use of sympathectomy with arterial grafting. In our initial work with arterial grafts I felt that where a good graft was inserted the use of sympathectomy was unnecessary. With further experience I now feel that wherever the condition of the patient justifies it, it is desirable to employ sympathectomy in conjunction with grafting, for several reasons. In the first place, it promotes maximal vasodilation in the affected extremity and therefore, I believe, promotes a maximum flow of blood and diminishes the chance of thrombosis within the graft. Secondly, in the event of ultimate closure of the graft or prosthesis, there may be less associated spasm in the extremity at this critical time and thus disaster in the form of tissue necrosis may be averted. Thirdly, in the event of closure of the graft, it eliminates the necessity for another operation and another anesthesia.

I should like now to summarize briefly the principal indications and contraindications for lumbar sympathectomy.

First, where any occlusive arterial disease exists and is static or progressively worsening, where claudication or ischemic neuritis is disabling and interferes with productivity, or where gangrene is impending, or where there is limited amount of tissue necrosis and where epidural anesthesia indicates improvement and the general condition justifies it, sympathectomy should be performed.

Second, sympathectomy is desirable wherever grafting is done to reestablish flow in the face of segmental occlusion. Where excellent distal pulses are immediately established, it may not be necessary. Where there is some doubt of distal flow, however, the sympathectomy should be done to secure maximal peripheral dilatation and maximal run-off.

Third, where severe vasospasm associated with hyperhidrosis is a serious problem, sympathectomy is of real benefit and should be offered.

Fourth, in the group of conditions which may be classified as post-traumatic sympathetic dystrophies associated with bizarre pain patterns and vasomotor imbalance, sympathectomy may be curative if performed early.

Fifth, in acute arterial occlusions, such as by embolus or trauma, where reconstruction or embolectomy is unavailing or for some reason impractical, and where spasm is obviously present as demonstrated by epidural block, lumbar sympathectomy may provide just enough additional flow to prevent the onset of gangrene.

On the other side of the picture, where gangrene has proceeded to a point where amputation is inevitable and where there is little likelihood of altering the level at which amputation will succeed, there is no indication for sympathectomy. If done, this simply adds an additional operation to a patient already in a high risk group, with too little payoff in the final result to justify it.

Further, where the so-called paradoxical effect is seen following block, that is, good proximal vasodilation with a worsening of the distal circulation, sympathectomy is contraindicated.

Finally, it is well to realize that there is a price to pay for sympathectomy. About one out of three patients, perhaps more, will suffer from post-sympathectomy neuralgia. This is always self-limited but may be extremely severe and incapacitating so that the procedure is not to be undertaken lightly.

In summary, a rational and simple approach to the use of lumbar sympathectomy in peripheral occlusive vascular disease of the lower extremities is presented. When properly used it is a very useful and, at times, a limb-saving device.

REFERENCES

1. Husni, E. A. and Simeone, F. A. Results of lumbar sympathectomy in peripheral vascular disease, *Arch. Surg. 75:* 530-41, 1957.

2. DeBakey, M. E., Creech, O. and Woodhall, J. P. Evaluation of sympathectomy in arteriosclerotic peripheral vascular disease, *J. Amer. med. Assoc. 144:*1227-31, 1950.

BOWEN-BROOKS SCHOLARSHIP
FOR ADVANCED STUDY ABROAD—1962-63

The New York Academy of Medicine

In the current year the Committee on Medical Education will award *one* Scholarship grant in the amount of $4,800.00 for the *academic year 1962-63*.

This Scholarship was established by the donor to provide aid for advanced study abroad in a clinical subject in preparation for the practice of medicine or surgery in any of their branches. As stipulated by the donor of the fund, candidates must be *male* interns or residents in voluntary, municipal or Veterans Administration hospitals in New York City.

The course of study, the auspices under which it is to be taken, and the place or places where study is to be pursued, must receive the approval of the Committee. Applicants are favored who, from their records, show themselves capable of advanced work in clinical medicine. The Committee stipulates that the study be pursued abroad, preferably in Great Britain or in continental Europe.

Applications for this Scholarship must be submitted by **September 1, 1961.** Candidates may secure application forms by addressing:

Aims C. McGuinness, M.D., Executive Secretary
Committee on Medical Education, The New York Academy of Medicine
2 East 103 Street, New York 29, N. Y.

Fifth Annual POSTGRADUATE WEEK
October 23 to 27, 1961

SURVEY AND REVIEW

The physiology, diagnosis and therapy of selected aspects of a specific disease will be presented each day. The program will include panel discussions and individual papers.

Morning Sessions: Daily 10 a.m. to 12 noon
Afternoon Sessions: Daily 1 p.m. to 3 p.m.
No Evening Sessions

A Subscription Luncheon will be served in the Presidents' Gallery at the Academy each day.

Registration

Members of the medical profession, including interns and residents, and those working in the allied sciences, are cordially invited to attend all sessions. Registration (*without fee*) is required for non-Fellows of the Academy.

A detailed program, when published, will be mailed to every Fellow of the Academy without request and to others on request addressed to:

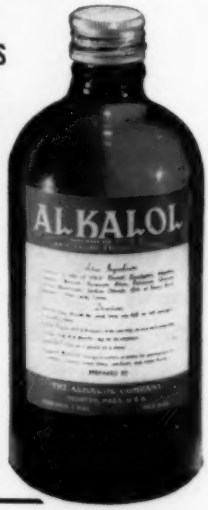
The Secretary, Postgraduate Week
The New York Academy of Medicine
2 East 103 Street, New York 29, N. Y.

ALKALOL

for cleansing in
BIOPSIES (Schiller Test)

MUCUS PLUGS
CAUTERIZATIONS

Alkalol is used as a cleansing agent in preparing the cervix for the Schiller Test. It is a mucus solvent whose low surface tension enables it to penetrate into and cleanse the folds of the vagina mucosa.



Write for sample

THE
ALKALOL COMPANY
Taunton 4, Mass.

BULLETIN

THE NEW YORK
ACADEMY OF MEDICINE

The Bulletin contains scientific papers presented at the Academy, including . . .

Post-Graduate Week Lectures
Stated Meeting Addresses of the Academy
Academy Section Papers
Monthly Panel Meetings—Transcripts
New York Pathological Society—Abstracts
and Other Original Contributions

Published Monthly

Annual subscription price, $8.00 in United States and Canada.
All other countries $9.00

BENDINER & SCHLESINGER

Laboratory

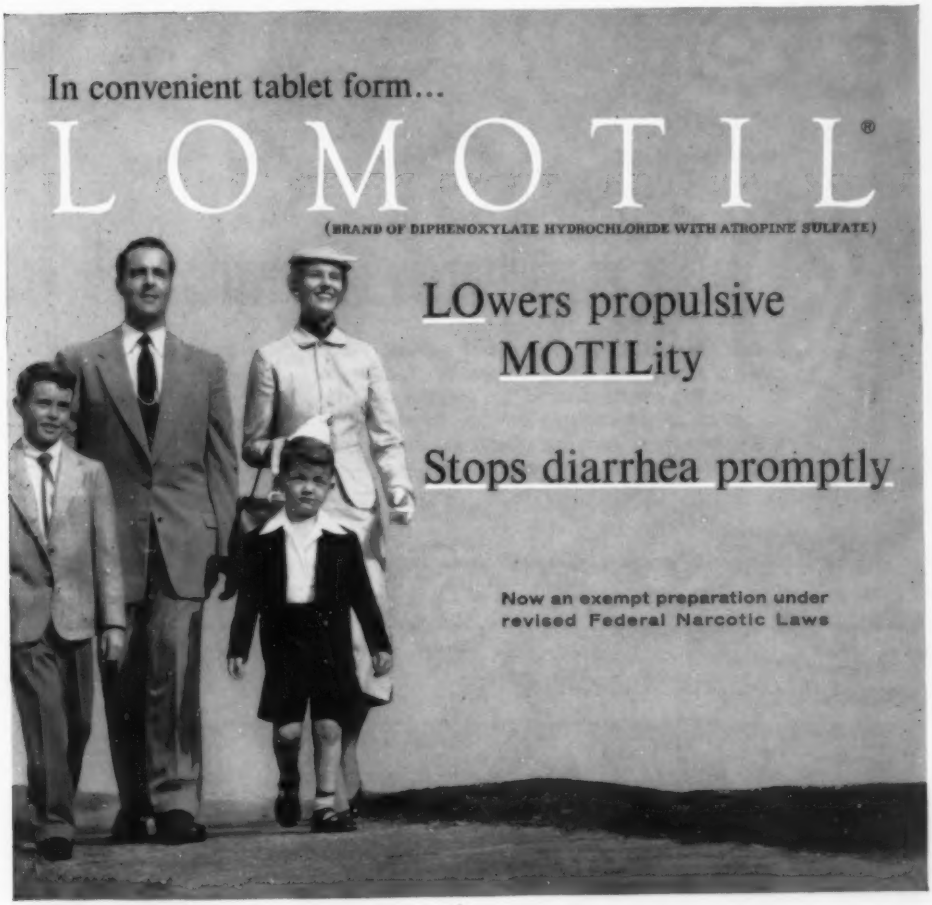
JOHN TENNYSON MYERS, M.D., Ph.D., *Director*

SERVING THE PHYSICIAN FOR OVER HALF A CENTURY IN THE CLINICAL LABORATORY FIELD.

Third Avenue and Tenth Street • New York City 3, N. Y.

Messenger Service—ALgonquin 4-2300

Also mailing facilities


In convenient tablet form...
LOMOTIL®
(BRAND OF DIPHENOXYLATE HYDROCHLORIDE WITH ATROPINE SULFATE)
LOwers propulsive MOTILity
Stops diarrhea promptly
Now an exempt preparation under revised Federal Narcotic Laws

Extensive clinical experience in the United States and Europe demonstrates that Lomotil provides prompt and positive symptomatic control of diarrhea.

Lomotil possesses a highly efficient antiperistaltic action. It controls diarrhea with few or none of the undesirable side effects of many other commonly used antiperistaltic agents.

In the control of diarrhea, Lomotil offers safety, efficacy and greater convenience.

DOSAGE: The recommended initial dosage for adults is two tablets (2.5 mg. each) three or four times daily, reduced to meet the requirements of each patient as soon as the diarrhea is under control. Maintenance dosage may be as low as two tablets daily. Lomotil, brand of diphenoxylate hydrochloride with atropine sulfate, is supplied as unscored, uncoated white tablets of 2.5 mg., each containing 0.025 mg. ($\frac{1}{2400}$ grain) of atropine sulfate to discourage deliberate overdosage.

Recommended dosage schedules should not be exceeded.

G. D. SEARLE & CO.
CHICAGO 80, ILLINOIS
Research in the Service of Medicine

Herald Square, N. Y. *Roosevelt Field, Long Island*

Parkchester, Bronx *Jamaica, Queens*

White Plains, N..Y. *Flatbush, Brooklyn*

MACY'S PRESCRIPTION DEPARTMENT

Macy's respects professional ethics. We carefully avoid discussing your prescription, either its ingredients or its use, with your patient. You can be assured that all your prescriptions are accurately compounded exactly as you write them. And all our preparations, made from the finest ingredients obtainable, are carefully checked by our supervising pharmacists.

No wonder so many physicians prefer Macy's Prescription Department.

Announcing

Walker-Gordon 900

A 900-CALORIE DIETARY FOOD FOR WEIGHT-CONTROL

When patients consult you concerning 900-calorie diets, please consider recommending Walker-Gordon's new "900," a milk-base food drink. The fluid milk used in this product is Walker-Gordon Certified, the World's Finest Milk. Delivered to homes by leading dairies, usually within 24 hours after milking. Excellent flavor and keeping quality. 2 flavors—chocolate or plain. Tell your patients to ask their own milkmen for home delivery. Write or phone for professional sample and complete information.

Produced - Pasteurized - Homogenized - Packaged at

WALKER-GORDON CERTIFIED MILK FARM

Plainsboro, N.J. • SWinburne 9-1234

New York: WAlker 5-7300 • Phila.: PEnnypacker 5-3465

ANNOUNCING... A POTENT ANTIDEPRESSANT WITH EFFECTIVE ANTI-ANXIETY PROPERTIES...

NEW

ELAVIL

AMITRIPTYLINE HYDROCHLORIDE

MSD

new...a potent antidepressant with effective anti-anxiety properties

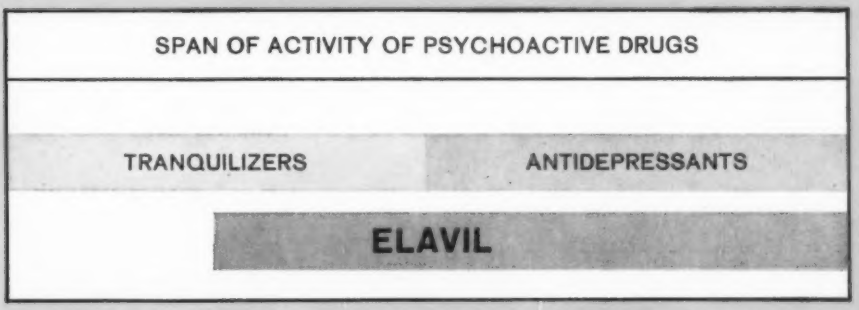
AMITRIPTYLINE HYDROCHLORIDE

RELATIVE UTILITY IN MANAGEMENT OF DEPRESSED PATIENTS

Class of compounds	TARGET SYMPTOMS OF DEPRESSION: *Anxiety*	*Insomnia*	*Depression*	*Over-all relief of symptoms*
TRANQUILIZERS	"Failure of the tranquilizers to produce satisfactory results is due in many cases to their being prescribed for depression, especially depression masked by the more prominent symptoms of anxiety. The underlying depression may be deepened."[1]			+ −
ANTIDEPRESSANTS			"CNS stimulants and anti-depressants, if given to anxious patients, will increase the anxiety...."[1]	+
ELAVIL	"...this drug [ELAVIL] acted both as a tranquilizer and as an anti-depressant...."[2] Many physicians customarily treat anxious or depressed patients with a combination of an antidepressant and a tranquilizer. This is seldom necessary when prescribing ELAVIL because it has both antidepressant and anti-anxiety properties.			++

AVIL.

effective in patients with depression...
particularly useful in those with predominant symptoms of anxiety and tension...provides prompt relief of anxiety and insomnia associated with depression



INDICATIONS: Manic-depressive reaction – depressed phase; involutional melancholia; reactive depression; schizoaffective depressions; neurotic depressive reaction; and these target symptoms: anxiety; depressed mood; insomnia; psychomotor retardation; functional somatic complaints; loss of interest; feelings of guilt; anorexia. May be used whether the emotional difficulty is a manifestation of neurosis or psychosis,[4] and in ambulatory or hospitalized patients.[3, 4, 5]

USUAL ADULT ORAL DOSAGE: Initial, 25 mg. three times a day, until a satisfactory response is noted. Many patients improve rapidly, although some depressed patients may require four to six weeks of therapy before obtaining maximum benefit. In severely depressed patients, as much as 150 mg. per day may be given. **Maintenance,** 25 mg. two to four times a day. Some patients may be maintained on 10 mg. four times a day. The natural course of depression is often many months in duration. Accordingly, it is appropriate to continue maintenance therapy for at least three months after the patient has achieved satisfactory improvement in order to lessen the possibility of relapse, which may occur if the patient's depressive cycle is not complete. In the event of relapse, therapy with ELAVIL may be reinstituted.

ELAVIL is not a monoamine oxidase (MAO) inhibitor. No evidence of drug-induced jaundice or agranulocytosis has been noted. Side effects (drowsiness, dizziness, nausea, excitement, hypotension, fine tremor, jitteriness, headache, heartburn, anorexia, increased perspiration, and skin rash), when they occur, are usually mild. However, as with all new therapeutic agents, careful observation of patients is recommended. As with other drugs possessing significant anticholinergic activity, ELAVIL is contraindicated in patients with glaucoma.

SUPPLY: Tablets, 10 mg. and 25 mg., in bottles of 100. **Injection** (intramuscular), 10 mg. per cc., 10-cc. vials.

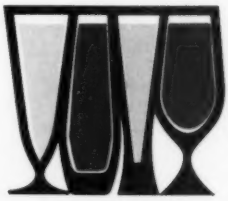
REFERENCES: 1. Perloff, M. M., and Levick, L. J.: Clinical Med. 7:2237, Nov. 1960. 2. Freed, H.: Am. J. Psychiat. 117:455, Nov. 1960. 3. Dorfman, W.: Psychosomatics 1:153, May-June 1960. 4. Ayd, F. J., Jr.: Psychosomatics 1:320, Nov.-Dec. 1960. 5. Barsa, J. A., and Saunders, J. C.: Am. J. Psychiat. 117:739, Feb. 1961.

Before prescribing or administering ELAVIL, the physician should consult the detailed information on use accompanying the package or available on request.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

ELAVIL IS A TRADEMARK OF MERCK & CO., INC.

introducing...nutritional support in convenient, tasty, liquid form to supplement inadequate diets... to replace skipped meals



Nutrament™

BRAND

nutritionally complete food

a nutritious meal, ready to drink

nutritional support is often needed for:

careless or irregular eaters—who skip breakfast or lunch or do not eat properly because of busy schedules or faulty eating habits.

children—who need increased basic nutrients during convalescence[1] or during difficult feeding periods, such as after tonsillectomies.[2]

adolescents—who require nutritional support because of growth needs and poor dietary selection.[3]

pregnant patients—who often require sound, easily tolerated, and convenient nutritional supplementation during pregnancy and lactation.[4]

geriatric patients and others—who cannot or will not maintain proper nutrition because of poor dentition, faulty eating habits, or lack of interest in eating.[5]

hospital patients—Nutrament liquid can serve as an excellent and convenient source of nourishment.

and in Oral, Dental or Surgical conditions—which interfere with or prevent consumption of solid food.

readily accepted by patients

Nutrament liquid requires no special preparation. Smooth texture and appealing taste of Nutrament make it readily acceptable. Equally delicious served hot or cold. Nutrament also has a high satiety value.

supplied

In 12½ fl. oz. cans, chocolate and vanilla flavors. Conveniently available at drug and food stores.

offers a scientifically balanced ratio of carbohydrate, protein, and fat. Each 12½ fl. oz. can of Nutrament liquid provides 400 calories. Caloric distribution: protein–20% (20 Gm.); carbohydrate–50% (50 Gm.); fat–30% (13.3 Gm.); plus the following vitamins and minerals:

		% MDR			
Vitamin A (U.S.P. Units)	1250	30	Vitamin E (Int. Units)	2.5	
Vitamin D (U.S.P. Units)	125	30	Pyridoxine, mg.	0.4	
Vitamin C, mg.	50	166	Vitamin B_{12}, mcg.	0.5	
Thiamine, mg.	0.5	50	Calcium pantothenate, mg.	2	
Riboflavin, mg.	0.6	50	Sodium, Gm.	0.2	
Niacinamide, mg.	5	50	Potassium, Gm.	0.9	
Calcium, Gm.	0.5	67	Copper, mg.	0.5	
Phosphorus, Gm.	0.4	53	Manganese, mg.	1	
Iron, mg.	4	40	Fiber, Gm.	0.55	
Iodine, mcg.	60	60			

ingredients: Whole milk, skim milk, sugar, soy flour, Dextri-Maltose® (maltose and dextrins derived from enzymic action of choice barley malt on selected corn flour), starch, chondrus extract, sodium alginate, vitamin A palmitate, calciferol, sodium ascorbate, thiamine hydrochloride, niacinamide, ferrous sulfate, sodium iodide, *d*-alpha-tocopheryl acetate, pyridoxine hydrochloride, cyanocobalamin, calcium pantothenate, salt, cupric carbonate, manganese sulfate, cocoa and/or imitation vanilla flavor.

references: (1) Nelson, W. E.: Textbook of Pediatrics, ed. 7, Philadelphia, W. B. Saunders Company, pp. 231-233, 1959. (2) Parrott, R. H., and Nelson, W. E.: *ibid.*, p. 759. (3) Johnston, J. A.: Ann. New York Acad. Sc. *69*:881-901 (Jan. 10) 1958. (4) Burke, B. S., and Kirkwood, S. B., in Greenhill, J. P.: Obstetrics, ed. 12, Philadelphia, W. B. Saunders Company, 1960, pp. 126-131. (5) Skillman, T. G.; Hamwi, G. J., and May, C.: Geriatrics *15*:464-472 (June) 1960.

87061

Edward Dalton Co.
A DIVISION OF
MEAD JOHNSON & COMPANY

Quality products from nutritional research

more than just vitamins A and D

DESITIN® ointment

also provides
unsaturated fatty acids as well as the vitamins A and D (of high grade Norwegian cod liver oil)—essential to skin health and integrity

and ingredients that are emollient, lubricant, gently astringent, protective, and aid tissue repair (zinc oxide, talcum, petrolatum and lanolin)

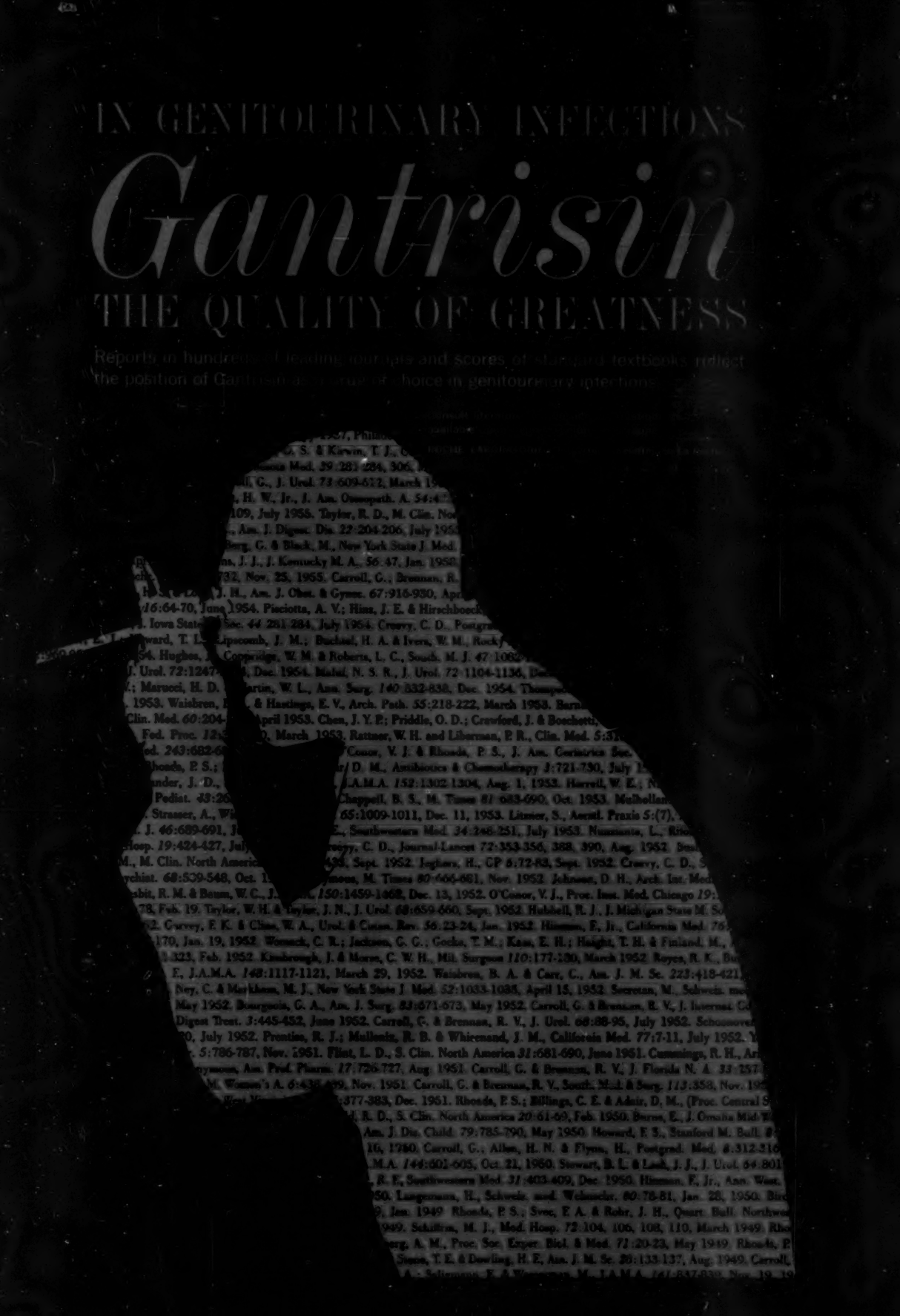
in a smooth creamy ointment so processed that one application of Desitin soothes, protects, and promotes healing for hours in . . .

diaper rash
wounds
burns
ulcers
(decubitus, diabetic, varicose)
intertrigo

Samples Please write . . . DESITIN CHEMICAL COMPANY
812 Branch Avenue, Providence 4, R. I.

IN GENITOURINARY INFECTIONS

Gantrisin

THE QUALITY OF GREATNESS

Reports in hundreds of leading journals and scores of standard textbooks reflect the position of Gantrisin as a drug of choice in genitourinary infections.